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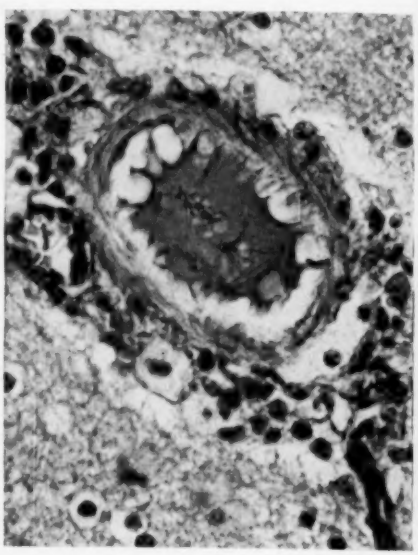

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A. M. A.
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NEUROHUMORAL FACTORS IN EMOTION

INTRODUCTION

THE ASSEMBLY of a large number of people with diverse interests at such a gathering as an international physiological congress is an opportunity for concerted discussion. In an attempt to provide a forum for review of subjects not listed in the formal seminars, the program committee delegated certain persons to organize panels in various areas. Since the word seminar was already employed on the program, the term Group Meeting was used to designate those meetings which occurred with the sanction of the Congress, but which were not listed in detail in the program. It was felt that the Group Meetings would provide an opportunity for certain persons with more or less specialized interest to meet with profit. So it proved. Having settled on a topic in the general area suggested to us, we approached those coming to the Congress whose interests we felt would integrate so that the papers would provide logical continuity. How close that aim was achieved the reader may judge, but the meeting attracted a large and attentive audience and received an enthusiastic reception.

It was a signal honor to have Prof. W. R. Hess as one of our speakers and to hear of his work at firsthand. Dr. G. W. Harris was unable to provide a manuscript of his remarks but permitted us to abstract a paper of his which covers essentially the same area. The difficult feat of appraisal of the four papers which comprise the body of the meeting was undertaken by Dr. Roy R. Grinker. In his judicial and discriminating remarks, one may discern some of the shortcomings, as well as the positive achievements, in the current scientific study of emotion.

R. A. CLEGHORN, M.D.
E. D. WITTKOWER, M.D.
For the Program Committee

Report on a Group Meeting held at the 19th International Physiological Congress, Montreal, Canada, Sept. 2, 1954.

PITUITARY-HYPOTHALAMIC MECHANISMS

G. W. HARRIS, M.D., Sc.D., Cambridge, England

I. THE NEUROHYPOPHYSIS

THE NEUROHYPOPHYSIS and the adrenal medulla are the only two endocrine glands dependent on a secretory nerve supply for their functional activity. It is only within relatively recent years that the mechanisms controlling the secretion in the neurohypophysis have been worked out. Observations of Ramón y Cajal, Pines, and Greving defined the tract of unmyelinated nerve fibers running from the paraventricular and supraoptic nuclei to the neurohypophysis. Ranson and his colleagues observed that fibers comprising the tuberohypophysial tract, of uncertain origin, ran in the dorsal wall of the hypothalamohypophysial tract, most of whose fibers came from the supraoptic nucleus. Lesions of the supraopticohypophysial tract made with the Horsley-Clarke stereotaxic instrument in cats were shown by Fisher, Ingram, and Ranson to lead to diabetes insipidus controllable by posterior pituitary extracts. Morphologically, atrophy of the neurohypophysis occurred, and the median eminence and infundibular stem and process became shrunken and hypercellular. The adenohypophysis was unaffected. These results were confirmed in the monkey, in which it was also shown that severance of the pituitary stalk produced little or no polyuria provided the median eminence escaped damage. Presumably, that tissue must elaborate antidiuretic hormone. The situation regarding the oxytocic fraction of the neurohypophysis is less clear. Most animals with the supraopticohypophysial tract divided have prolonged labor or dead fetuses.

The mechanisms by which changes in the environment, emotional stimuli, or blood osmotic pressure changes affect the urine flow by changing the rate of secretion of the antidiuretic hormone have been investigated by Verney. All these seem to exert their effect through excitation of the supraoptic nuclei. The inhibition of water diuresis, which normally occurs with an emotional stimulus, can, curiously enough, be prevented by a small prior dose of epinephrine. The "physiological diabetes insipidus" which follows ingestion of water is due to decrease in osmotic pressure of the blood acting on receptive elements probably situated in the highly vascular supraoptic nuclei. Some of the fibers synapsing in the supraoptic nuclei are cholinergic, responding to injected acetylcholine or nicotine by an inhibition of water diuresis.

Stimulation of the supraopticohypophysial tract without anesthesia and by the remote control method developed by Harris showed that the neurohypophysis so stimulated released antidiuretic and oxytocic substances. In the natural state, stimulation of vulval erectile tissue in the estrus rabbit results in an increase in activity of the empty uterus, which facilitates the passage of sperm to the tubal ends of the uterus. This stimulus invokes the supraopticohypophysial tract and only oxytocic secretion, for with coitus the antidiuretic fraction is not secreted. This act does, however, lead to release of luteinizing hormone from the adenohypophysis, which causes ovulation.

In the process of lactation the neurohypophysis is also involved, particularly the phase of milk discharge. Petersen provided evidence that oxytocin excited, and epinephrine or fright inhibited, the "let-down" in the two halves of a cow's udder, one-half of which was denervated. Cross and Harris showed

Abstract of articles, References 1 and 2.

Read in the Group Meeting on Neurohumoral Factors in Emotion at the 19th International Physiological Congress, Montreal, Canada, Sept. 2, 1954.

that the supraopticohypophysial tract was an essential link in the reflex nervous release of oxytocin by the stimulation of the nipples by suckling. Without this hormone to stimulate myoepithelial cells of the mammary alveoli, the young cannot obtain milk despite vigorous sucking. The results throw light on the known aid to uterine involution occurring with breast feeding.

II. THE ADENOHYPOPHYSIS

The adenohypophysis and its dependent target glands, e. g., thyroid, adrenal cortex, and gonads, have no well-defined innervation but are nevertheless influenced by nerve processes. A great variety of stressful external stimuli or disturbing emotions may influence the secretory activity of the adenohypophysis by way of the hypothalamus and pituitary stalk. For this, none of the known nerve pathways, sympathetic, parasympathetic, or the hypothalamohypophysial tract in the pituitary stalk, are essential, and separation of these nerve tracts is quite compatible with normal function of the adenohypophysis. The link whereby stimuli from the hypothalamus reach the anterior pituitary is a vascular one, first described by Popa and Fielding as a series of portal vessels connecting capillaries in the adenohypophysis to capillaries in the tuber cinereum. Wislocki confirmed the main anatomical features of this system but drew what is now believed to be the correct conclusion concerning the direction of blood flow, namely, from the hypothalamus to the gland. Green and Harris studied this area in many mammals and compared the vascular supply of the adenohypophysis to that of the liver, with the systemic arterial supply coming from a branch of the internal carotid, the portal supply from the so-called hypophysial portal vessels (running from the median eminence of the tuber cinereum to the anterior lobe of the pituitary), and a systemic venous drainage flowing laterally to the neighboring venous sinuses. The more intimate character of the portal blood can be described as follows: Small branches from the internal carotid and posterior communicating arteries supply the pars tuberalis (which embraces the median eminence) with a rich vascular plexus. From this many wide capillary loops penetrate into the median eminence, where they are intimately related with nerve fiber endings of the hypothalamohypophysial tract. These loops drain into large portal vessels, which run down the pituitary stalk to break up into the capillaries and sinusoids in the adenohypophysis. Thus is provided the means whereby chemical transmitters from the hypothalamus may be conveyed to the pars distalis of the hypophysis.

Hypothalamic stimulation by the remote-control technique enabled Harris to demonstrate that excitation of the tuber cinereum, particularly the posterior part, for as little as three minutes resulted in a full ovulatory response in the rabbit, which normally ovulates only after coitus. Even more prolonged stimulation of glandular segments, including the infundibular stem, was ineffectual.

The technique of transplantation of the hypophysis of rats further demonstrated the dependence of the adenohypophysis, and, in turn, its dependent target glands, on the intactness of the portal vascular connection with the tuber cinereum. Hypophysectomized rats whose anterior pituitary tissue was grafted into the subarachnoid space under the median eminence regained normal endocrine function as the graft was revascularized by the growth of portal vessels from the median eminence. The normality of function was demonstrated by regular estrous cycles, pregnancy, milk secretion, and a normal weight and histological picture of the ovaries, thyroid, and adrenal cortex. Controls whose graft was as well vascularized and viable in the subarachnoid area under one temporal lobe showed no estrous cycles, and the ovaries, thyroid, and adrenals were atrophic. This, then, is strong supportive evidence in favor of the view that stimuli to the adenohypophysis normally derive from the hypothalamus and are necessary for normal functioning of that tissue, and that the location of successful grafts under the temporal lobe

is too remote for the hypothalamic substances to have an effective influence. The nature of the chemotransmitters from the hypothalamus is not well elaborated. On the basis of extensive studies, Markee and his associates believe that it is an adrenergic substance transmitted by the portal vessels that liberates luteinizing hormone from the anterior pituitary. A large body of evidence marshaled by Long and his co-workers from studies on experimental animals indicates that epinephrine may play an important role in the release of corticotropin by the adenohypophysis. A wide variety of stresses which produce excitation of the sympathetic nervous system have been shown to result in reduction in cholesterol and ascorbic acid content of the adrenal cortex. There is also evidence that a strong audiogenic stimulus in rats produces an intense discharge of corticotropin and that this is not affected by the removal of the adrenal medulla. This work by Fortier is supported by observations of Vogt's which indicate that mild emotional stimuli cause a fall in adrenal ascorbic acid even after demedullation of the gland. That corticotropin secretion is regulated by the blood level of adrenocortical hormones has been proposed and strongly argued by Sayers. Injections of cortical hormones lead to adrenocortical atrophy, and pretreatment with such hormones prevents the usual fall in adrenal ascorbic acid to a variety of stresses. The conclusion is that stress stimuli increase the utilization of cortical hormones by peripheral tissues and that the resultant fall in blood hormone level stimulates corticotropin production by the adenohypophysis, which an excess prevents. Histamine has also been shown to cause a release of corticotropin.

Hypothalamic control of corticotropin secretion is implied in the experiments of Harris, using remote-control stimulation of the posterior region of the tuber cinereum or mammillary body of the rabbit. The lymphopenia that resulted was similar in its magnitude and time relations to that evoked by emotional stress or intravenously injected corticotropin. Other hypothalamic areas and the pituitary did not give this effect. Similar results were obtained by Hume in the unanesthetized dog. Lesions of those areas which when stimulated give a lymphopenia response were found by de Groot and Harris to prevent emotional stress lymphopenia. In support of the view that the hypothalamus acting by way of the hypophysial portal vessels affects the secretion of corticotropin is the finding of normal adrenal glands in rats with portal revascularized hypophysial grafts under the tuber cinereum, as compared with the atrophic adrenals occurring in rats with intact vital grafts remotely situated from the hypothalamus.

It seems, then, that the basic steady output of corticotropin is dependent on the pituitary having an intact vascular connection with the hypothalamus. The probability is that the blood level of adrenocortical hormones also exerts control of corticotropin output by an effect on the hypothalamus. This is similar to the situation with respect to gonadotropic secretion, in which maintenance of reproductive processes depends on hypothalamic control of the adenohypophysis via the portal blood vessels. Gonadal secretions, in turn, act on the hypothalamus, whose activity may, in turn, be modified by environmental and emotional stimuli. Barbiturate drugs, which have a selective action on the hypothalamus, block or modify the release of corticotropin and luteinizing hormone.

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EXPERIMENTAL DATA ON ROLE OF HYPOTHALAMUS IN MECHANISM OF EMOTIONAL BEHAVIOR

WALTER R. HESS, Zürich, Switzerland
and
KONRAD AKERT, Baltimore

THE TECHNIQUE of electrical stimulation of subcortical structures developed by one of us (Hess *) is particularly suited to studies of the central organization of behavioral mechanisms. In the sequence of systematic investigations of the diencephalon and adjacent structures of the forebrain and mesencephalon (summarized by me [13] in 1949) several thousand "points" were explored. The effects of electrical stimulation (cinematographically recorded) were correlated with the localizations of the needle tips (controlled by histological analysis). Among the various effects elicited were some, of particular note, which consisted of characteristic changes in the total attitude of the animals. The changes observed were best compared with alterations seen in emotional states of normal animals, such as fear, anger, and pleasure, or with certain drives, such as explorative tendencies, feeding tendencies, cleaning tendencies, and continuous restlessness. The question may arise here as to whether the described phenomena were accompanied by the subjective experience which is generally termed "emotion." Several authors, since Sherrington [17] (1904), have been inclined to differentiate experimentally induced responses from normal behavior in terms of "pseudoaffect," "sham rage," etc. This differentiation, however, does not apply to our observations, since the reactions of the animals during hypothalamic stimulation differed in no way from those observed under normal environmental conditions. Although such terms as "feelings" and "emotion" are subjective categories, and ultimately beyond the limits of objective control, our observations are termed "emotional" changes, since they are based on criteria identical with those conventionally applied in animal and human psychology to the phenomena of expressional mechanisms.

A typical example of an emotional response obtained by electrical stimulation of the hypothalamus is represented by the syndrome of the "affective defense reaction" (Hess †). In this syndrome the animal assumes a typical defense posture, extends the claws, and lashes the tail. The syndrome is further characterized by hissing, spitting, and growling; by wide-open pupils and eyes; retraction of the ears; a bushy tail, and piloerection of the back. At this stage of general excitement a slight move on the part of an observer is sufficient to make him the object of a brisk and well-directed assault. The sharp teeth and claws are effectively utilized in this attack. The build-up of the defense reaction, if threshold stimuli are applied, takes three to eight seconds. At the end of the stimulation there is a rapid breakdown of the syndrome. Even the most impulsive attack is stopped and the animal as a rule is willing to be petted. But the threshold of angry behavior is maintained at a low level for a longer period. The histological control, according to Hess and Brügger,[11] identifies the active area of the described response within the perifornical area of the hypothalamus. Positive results were also obtained in the preoptic and ventral septal region and in the central (periaqueductal) gray matter of the midbrain. In contrast, comparative stimulation studies identified a large number of diencephalic and telencaphalic regions which

Read in the Group Meeting on Neurohumoral Factors in Emotion at the 19th International Physiological Congress, Montreal, Canada, Sept, 2, 1954.

* References 10 and 13.

† References 9, 11, and 12.

did not produce emotional responses: dorsal thalamus (Hess [13]), striatum (Akert and Andersson [1]), cornu Ammonis and mammillary bodies (Akert and Andy [2]), anterior limbic and orbitofrontal cortex (Hess, Akert, and McDonald [14]). In summary, electrical stimulation of circumscribed hypothalamic areas induces a typical change in behavior which is characterized by a spatial and temporal integration of somatomotor and autonomic mechanisms. It reminds the observer of the behavioral pattern displayed by a normal cat when confronted with a barking dog (enemy).

It becomes apparent from these findings that the hypothalamus plays a specific and prominent role in the organization of the affective defense reaction. This is in keeping with the well-known experimental work of Bard,‡ who has demonstrated that chronic decerebrate animals still display well-integrated angry behavioral patterns as long as certain parts of the hypothalamus are left in connection with the remaining brain stem. An analogous experiment was recently carried out in Bard's laboratory (Akert §) in which a bilaterally neodecorticated cat ‖ was stimulated with implanted Hess electrodes in the perifornical area. A full-blown affective defense reaction was obtained at the usually low threshold; no directed attacking mechanisms were observed under these conditions. From these and many other observations (Ranson,[16] Grinker,[8] Wheatley,[18] and Ingram [15]) it seems fair to conclude that the hypothalamus holds a unique position among the structures which cooperate in the organization of behavioral patterns. It is considered the one in particular which maintains the most direct connections to the main effector mechanisms. This relationship apparently is based upon a very stable and rigid organization which, as indicated in the case of electrical stimulation, as well as in Bard's midbrain animals, exhibits a rather stereotyped response, regardless of the degree of differentiation of the inductory signals. The problem arises as to whether there exists an internal topographical arrangement of the hypothalamic "center" which would be consistent with specific downstream projections to the single effector systems. As yet such an arrangement has not been found.

Along with the affective defense reaction, other behavioral changes consequent to hypothalamic stimulation have been observed, as mentioned above (Brügger [7]). In many respects the general role of the hypothalamus in the organization of these mechanisms seems analogous to that exemplified in the defense reaction.

A moving picture was shown ¶ demonstrating (1) the affective defense reaction elicited by hypothalamic stimulation in a freely moving animal, and (2) the same reaction obtainable after removal of the major parts of the neocortex and after removal of the mammillary bodies.

‡ References 3, 5, and 6.

§ Akert, K.: Unpublished data.

‖ The animal was prepared by Dr. E. Henneman, Baltimore.

¶ The moving picture was prepared partly in the Department of Physiology, University of Zürich; partly in the Department of Physiology, The Johns Hopkins University, Baltimore.

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THE LIMBIC SYSTEM ("VISCERAL BRAIN") AND EMOTIONAL BEHAVIOR

PAUL D. MacLEAN, M.D., New Haven, Conn.

THE LIMBIC system is comprised of the great limbic lobe of Broca and its subcortical cell stations. The limbic lobe, including the infolded hippocampus, was so named by Broca because it completely surrounds the hilus of the hemisphere. Its subcortical cell stations include the amygdala, the septal nuclei, the hypothalamus, the anterior thalamic nuclei, parts of the basal ganglia, and perhaps also the epithalamus. As Broca pointed out, the limbic lobe forms a common denominator in the brains of all mammals. In accordance with the theory of Papez, the experimentation of the last 15 years suggests that the limbic lobe also provides a cortical common denominator for a variety of emotional and viscerosomatic reactions in the mammal. Its relative constancy of gross and microscopic structure throughout the phylogeny of the mammal contrasts strikingly with the structure of the neopallium that mushrooms around it. The latter, some might argue, could be likened to an expanding numerator, representing in phylogeny the growth of intellectual functions. It is because of the inferred primacy of the role of the limbic system in emotional behavior that in psychiatric parlance I have used the term "visceral" in its original 16th century meaning and have applied it in quotation marks to the brain included in this system.

I wish to discuss some recent findings pertaining to the hippocampus and its associated structures in the hippocampal formation and suggest some implications of this material in regard to emotional mechanisms. In the microcosm of the brain there is hardly a structure that has left us more at sea regarding its functions than the hippocampus. This structure is so large in the brains of all animals and bears such a strategic relationship to the heart of the limbic system that we may well afford to devote especial attention to studies that can shed any light at all on its physiology.

In man the bulk of the hippocampal formation, including the hippocampus, hippocampal and dentate gyri, and amygdala, is found in the mediobasal part of the temporal lobe. In a psychophysiological review of the limbic system in 1949, I presented a diagram to illustrate the possible convergence of the interoceptive and exteroceptive systems in the hippocampal formation. It was inspired by discussions with Dr. Papez and was based on a number of fragmentary anatomical and physiological observations. From the cytoarchitectural studies of Lorente de Nó, one finds there is an overlapping of incoming systems into the hippocampal gyrus. Hence, in the diagram there was indicated an overlapping of impressions coming from the mouth, nose, viscera, sex organs, eye, ear, and body wall. It was emphasized that this part of the brain, in contrast to the neopallium, has strong connections with the hypothalamus.

Generally speaking, the limbic cortex can be distinguished from the surrounding neopallium by (1) the absence or poorer development of the supragranular layers, (2) the ending of the afferent plexus in the superficial layers, and (3) the relative paucity of cells of short axon. These phylogenetically primitive characteristics are nowhere better demonstrated than in respective parts of the hippocampal formation. The foregoing considerations, in conjunction with

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the emotional changes presumably associated with disease or experimental manipulation of this part of the brain, were the basis for the suggestion that the structures making up the hippocampal formation derived information largely in terms of feeling.

No experiment is so compelling as the one contrived by nature to support the thesis that this part of the brain allows a confluence of the bodily senses and imparts to them the quality of feeling. Epileptogenic foci here or in closely related cortex are known to be associated with a wide variety of auras, involving all the body senses and a great number of feeling and emotional states. But it is only recently that physiological studies have borne out the claims of comparative neurology and demonstrated that senses other than olfaction are afferently related to this region.

RESPONSES OBTAINED IN HIPPOCAMPAL FORMATION BY STIMULATION OF SENSORY SYSTEMS

There is now evidence that spike potentials may be evoked in respective parts of the hippocampal formation by vagal, auditory, visual, and somatic stimulation. On the other hand, Horwitz, Robinson, and I were struck to find that either gustatory or noxious stimulation resulted in trains of rhythmically recurring potentials in the pyriform area of the rabbit, somewhat like those induced by olfactory stimulation and first described by Adrian. In discussing the possible significance of the prolonged rhythmic responses elicited by olfactory, gustatory, and painful stimulation, it was pointed out that all three of the involved senses accent the intensity and quality of a stimulus rather than its spatial relationships. It is also of interest to note that emotion, which is frequently experienced in conjunction with discharges in this part of the brain, is like these other senses in so far as it is registered in terms of quality and intensity.

Evidence is accumulating that rhythmic responses (usually of a slower frequency) may also be recorded from the hippocampus subsequent to several forms of sensory stimulation. Over 14 years ago, Jung and Kornmüller reported that synchronized activity of about 6-per-second frequency occurred in the hippocampus of the waking rabbit when the animal received a hard pinch. We have observed synchronized activity in the hippocampus of both rabbit and cat following natural olfactory stimulation, but only rarely after gustatory stimulation. At the present Congress, Green and Arduini are scheduled to give a paper in which they will report that physiological stimulation of olfactory, visual, auditory, and somatic receptors in rabbit, cat, and monkey may evoke trains of 3- to 6-per-second potentials in the hippocampus. Recently, Liberson and Akert have reported that synchronized activity of about 6 per second may be recorded from the hippocampus of the guinea pig when the animal is alerted to the presence of the experimenter.

Thus, in addition to cytoarchitectural differences, one finds there are bioelectrical findings that justify the conclusion that the mechanism of communication in the phylogenetically primitive cortex is markedly unlike that in the neopallium. What these differences mean in terms of feeling (emotion) and intellect remains to be ascertained, but it is obviously of no little significance that such states as pain and attention, which bring about desynchronization of neocortical activity, result in synchronization of the activity in the hippocampal formation. From reading the abstract of the paper to be given by Green and Arduini, one gathers that there is a physiological support for previously vague inferences of a close tie-up between the ancient matrix of the reticular system and limbic structures.

ABLATION STUDIES

To date, experiments aimed at the ablation of the hippocampus alone, or severance of its projections by way of the fornix, have revealed disappointingly little in the way of behavioral changes. On the other hand, several workers have variously observed mani-

festations of the Klüver-Bucy syndrome when lesions are restricted to parts of the rostral hippocampal formation (amygdala, pyriform cortex, and contiguous part of the hippocampus). Conspicuous among the reported changes are (1) an apparent taming of a wild animal, (2) a tendency of the animal to examine everything with the mouth, (3) a failure to persist in avoiding noxious stimuli, (4) an alteration in dietary habits, and (5) bizarre sexual behavior. It is interesting that excision of cortex which yields the prolonged rhythmic responses upon olfactory, gustatory, and noxious stimulation appears to be correlated with the animal's change in dietary habits and his tendency to expose himself again and again to painful stimuli.

STIMULATION STUDIES

Studies employing stimulation in the intact, unrestrained, and waking animal have elucidated to a considerable extent the part that the rostral hippocampal formation plays in general behavior. Since much of this work has already been reviewed, I shall pause only to say that evaluation of all the results would seem to indicate that this frontotemporal portion of the limbic system is concerned with the organization of the oral activities of the animal as they pertain to eating, and to the vocalization, attack, and defense involved in obtaining food.

Stimulation studies, however, have thus far been a little more successful than ablation methods in indicating the functions of the bulk of the hippocampal formation lying posterior to the portion just considered. In a continuation of our electrical and chemical stimulation studies on the limbic system, I have focused attention particularly on the body proper of the hippocampus. With electrical stimuli too weak to elicit an after-discharge, responses most commonly seen in the cat are some contraversive movements of the head and ipsilateral closure of the eye. In some instances, possibly because the electrodes infringe on fimbrial fibers from the rostral hippocampus, one can elicit cringing, defensive attitudes, in which there is a retraction of the ipsilateral ear, a wrinkling of the face, and a pulling of the head away from the stimulated side. Rarely, one hears miaowing or a hiss.

On the other hand, dramatic changes are seen during after-discharges which follow stimulations of greater strength. Any turning movements that were present during the initial stimulation appear to reverse themselves with the onset of the after-discharge, and the pupils may suddenly dilate. Purring, if previously present, may cease and be replaced by occasional miaows or yowls. Concurrently, the animal assumes attitudes that strike one at first as being rapt attention or fearful alerting for the unexpected. Further examination indicates, however, that the animal is poorly in contact with his environment. Although the pupils react to light, the animal will not avoid the light, nor will he cringe when one pretends to strike the face. If one forcefully blows smoke at him, he will withdraw a little but will not avoid the smoke. A burning cigarette may be brought up to his nose with no response, but if there is a momentary contact with the lighted end, the animal may lunge about wildly. The emotional changes that one may induce during an after-discharge are most interesting: If one takes an animal which prior to stimulation simply miaows when the tail is pinched, one finds that the same noxious stimulus may cause him to hiss, spit, and strike out during the after-discharge. A prolonged or repeated noxious stimulus may lead to states of wild excitement, accompanied by spitting and hissing. I have held on to the tip of the tail of such an animal and observed a state of rage in which he would not properly orient his attack, but, rather, would viciously bite at the stump of his tail. It is striking that these excited states may suddenly terminate in rather prolonged catatonic-like stances. A miaow or a series of miaows usually signal the end of the after-discharge.

Except for an apparent enhancement of grooming and pleasure reactions, excitation of the posterior hippocampus of the cat by local injection of acetylcholine (together with

physostigmine) or methacholine (Mecholyl) results in little spontaneous change of behavior that can be correlated with the altered bioelectrical activity in this structure.* It may be significant that two mean and fearful animals I was obliged to use, owing to a shortage of cats, never manifested spontaneous or induced pleasure reactions until there was bioelectrical evidence of excitation of the hippocampus. On the other hand, the local injection of such a potent cholinergic drug as carbachol U. S. P. (Doryl) gives one the opportunity to observe during a period of two hours or more many of the changes that are seen accompanying the after-discharges produced by electrical stimulation. When the intense seizure activity produced by this drug begins to abate, the animal may manifest enhanced pleasure reactions.

PROPAGATION OF HIPPOCAMPAL AFTER-DISCHARGES

A discussion of some of the foregoing findings will be postponed until we have considered the propagation of after-discharges that are initiated in the limbic system. Kaada has made the highly significant observation that such seizure activity has the tendency to spread in and be largely confined to the limbic system. In regard to the hippocampus, Kaada states that "after-discharges [initiated there] . . . readily spread into the entire limbic cortex of both sides, and further to the cortex just lateral to the rhinal fissure." His observations were made in anesthetized animals. In the waking, drug-immobilized animal, one can demonstrate a comparable situation. It is only with stronger stimulation that one finds a further spread of the discharge into the cortex of the lateral convexity. It is to be emphasized that there may be a propagation of hippocampal discharges without a discernible alteration of neocortical activity.

* A method had to be devised that circumvented the leaking back of these drugs along the injecting needle into the ventricle. In the latter event the cat may manifest growling, hissing, and savage behavior.

DISCUSSION OF STIMULATION AND ELECRO-ENCEPHALOGRAPHIC STUDIES

From the mapping of the after-discharges, one gets the impression that there exists a potential "schizophysiology" of the neopallium and the limbic cortex. This is fraught with significant implications that bear both on the behavioral changes accompanying induced hippocampal seizures in the animal and on certain epileptic and psychopathological conditions in man.

The sudden explosion of fury that can be induced in the animal during hippocampal seizures calls to mind the behavior of some patients with psychomotor epilepsy when an effort is made to impede their course of action during a seizure. On the other hand, the cat's equally sudden shift from wild excitement to frozen immobility is reminiscent of the behavioral fluctuations of patients with catatonic schizophrenia. We have not yet mapped the spread of hippocampal after-discharges in an animal thrashing about after the application of a noxious stimulus. One does not know, therefore, whether or not it is primarily dysfunction within the limbic and closely related systems that allows the development of the phenomena in question. The latter give the impression of corresponding to alternating states of massive release and inhibition, respectively.

It is possible that seizure activity that is largely confined to the limbic system may have a bearing on some of the epileptic behavior, as well as the postepileptic amnesia, of patients with psychomotor epilepsy. For illustrative purposes, it will be sufficient to cite a single case, and one which is generally familiar. This is Hughlings Jackson's famous Case Z, in which are described the seizures of a young doctor who at autopsy was found to have a small area of softening in the region of the uncinate gyrus. During a fit he was able to stoop over and pick up a pin or to continue the physical examination of a patient and to write a reasonable diagnosis, all with subsequent amnesia for what had happened. It strains the imagination to conceive how such acts requiring both manual

and intellectual skill could have been performed in the absence of a functioning neocortex. That seizure activity may take place in the limbic system without appreciable alteration of the neocortical activity possibly gives some insight into the mechanisms of such epileptic behavior.

But why the subsequent amnesia? In discussing the symbolic process, Kubie has emphasized that memory is dependent on the interplay of intrabodily and externally derived experience. He refers to the former as the gut component of memory. The limbic cortex is strongly related to the hypothalamus, which, to use Le Gros Clark's phraseology, is concerned "with all sorts of visceral and metabolic processes" that in their totality enable the organism "to appreciate itself as a unified being." Furthermore, neuronographic studies indicate that the posterior part of the hippocampal formation is but one synapse removed from a large expanse of parieto-occipitotemporal cortex to which Penfield ascribes the functions of memory and dreaming. Kubie, as the result of some collaborative studies with Penfield, has suggested that in the transitional region of the limbic and temporal cortex there may be an amalgamation of the gut component and the verbal component of memory, the place where the "I" and the "non-I" meet. From the foregoing considerations, might one infer that the experiences during a psychomotor seizure are lost to recollection because the limbic discharges interfere particularly with the recording of internally derived impressions?

SUMMARIZING COMMENT

Experimentation of the last 15 years suggests that the limbic system, which anatomically is a common denominator in the brains of all mammals, is also, physiologically speaking, a common denominator of a variety of viscerosomatic and emotional reactions. In this paper, especial attention is given to the recent developments pertaining to the part of the limbic system contained in the hippocampal formation. Bioelectrical studies are cited that provide further evidence that this part of the brain is afferently related to all the sensory systems. From these and other experiments concerned with ablation and stimulation, inferences are derived that give additional support to the theory that this region of the brain is concerned with the experience and elaboration of emotion.

REFERENCE

The need for economy of space precludes the listing of references to the extensive literature on which this paper is based. They may be found in the following publication, which deals more fully with the same material:

MacLean, Paul D.: The Limbic System and Its Hippocampal Formation: Studies in Animals and Their Possible Application to Man, J. Neurosurg. **11**:29-44, 1954.

SECRETION OF ANTIDIURETIC HORMONE IN RESPONSE TO NOXIOUS STIMULI

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THE CLASSIC studies of Verney and his associates reveal that exposure to physical or emotional stimuli which are noxious to animal or man results in an inhibition of the diuresis induced by the ingestion of water. A marked diminution in the rate of urine production occurs in animals exposed to such varied stimuli as severe exercise, surgical trauma, mechanical shaking, flashing lights, histamine, and so forth. In fact, the same stimuli which can initiate the sequence of events described by Selye as the "alarm reaction" elicit also an antidiuretic response. Extracts from the hypothalamus of such stressed animals exhibit a marked diminution in the concentration of antidiuretic hormone.

Direct evidence that an increase in the antidiuretic activity of the blood occurs when an animal is exposed to a noxious stimulus was not available until recently. With the development of a relatively simple, sensitive, and precise procedure for the assay of antidiuretic substances (ADS) in the blood plasma, it became possible to determine the activity of the plasma of animals and men exposed to noxious stimuli.

Pain, noise, injection of histamine, and exposure to a strange environment were employed as noxious stimuli for evoking an antidiuretic response in rats. Pain was produced by exposing each rat in a small metabolism cage to a two-minute period of repetitive mild electric shocks to the feet via a grid which made up the floor of the cage. Two groups of rats were given water by stomach tube, and the rate of excretion was noted. Whereas the two groups excreted urine at the same rate during the control period, a marked diminution in the rate of excretion occurred in the group which was exposed to the painful stimuli for two minutes.

A marked increase in the antidiuretic activity of the plasma was observed in rats exposed to the painful stimuli. Within 0.5 minute after such exposure, the plasma antidiuretic activity rose from the equivalent of 18.4 ± 1.4 milliunits of pitressin per 100 ml. to 64.3 ± 6.0 milliunits per 100 ml. Five minutes after such exposure, the ADS titer of the plasma fell to 43.9 milliunits; in 10 minutes, it was 36.2 milliunits and in 15 minutes it was 24.8 milliunits. Thus, exposure to the painful stimuli induced an extremely rapid increase in the antidiuretic activity of the plasma, and then a more gradual diminution ensued.

Similar studies were performed with rats exposed for five minutes to the noise produced by a Federal siren. Fortier has demonstrated that activation of the adrenal cortex occurs in rats exposed to such noise for 30 minutes. As with pain, exposure to noise for even five minutes resulted in a marked increase in the antidiuretic activity of the plasma. Subsequently, a gradual decrease ensued.

The intraperitoneal injection of 1 mg. of histamine hydrochloride per 100 gm. of body weight results in activation of the anterior pituitary gland of rats. The same quantity of histamine produced a marked increase in the antidiuretic activity of the plasma. Since the concentration of ADS in the plasma of groups of rats bled at intervals after the injection of saline remained unchanged, all control values were pooled. Whereas the ADS titer of the saline-injected animals was 20.9 milliunits per 100 ml., that of the hista-

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mine-treated rats was 63.7 milliunits in five minutes, 56.7 milliunits in 10 minutes, 47.7 milliunits in 15 minutes and 31.4 milliunits in 30 minutes. The difference between the controls and the histamine-treated rats was statistically highly significant except for that between the controls and the rats bled 30 minutes after the injection of histamine.

In order to test the effect of an emotional stimulus on the antidiuretic response, rats were placed individually into a two-compartment conditioning box for variable periods of time. The two ends and the top of the box were white; one side consisted of white milk glass, through which illumination was provided, and the remaining side consisted of a black one-way vision screen. This box was regarded as a strange environment for rats. Introduction of rats into this strange environment produced no overt behavioral responses other than defecation and an increase in grooming activities, such as have been utilized as a measure of emotionality of rats. As controls, rats were handled but not put into the box. No effect of exposure to the strange environment was noted in rats exposed for less than two minutes. The antidiuretic activity of the plasma of rats exposed to the box for two and three minutes differed significantly from rats exposed for shorter intervals. Even after 10 minutes of exposure, the activity remained elevated.

Having demonstrated that sensory stimuli (pain and noise), systemic stimuli (histamine), and emotional stimuli (strange environment) induce a rapid secretion of an antidiuretic substance into the circulation which resembles the antidiuretic hormone, it became pertinent to demonstrate the roles of the adrenal and pituitary glands in this process. Toward that end, the response of rats was studied 18 hours and 7 days after adrenalectomy. Although the activity of the plasma of the untreated 18-hour adrenalectomized rats was significantly greater than that of normal rats, exposure to painful stimuli resulted in a further increase. Such exposure also increased significantly the antidiuretic activity of the plasma of cortisone-treated 18-hour and 7-day adrenalectomized rats. Consequently, it may be concluded that the adrenal gland is not essential to the antidiuretic response to noxious stimuli.

The effect of hypophysectomy was then determined. As was noted by others who studied the antidiuretic activity of serum and urine, complete hypophysectomy results in a statistically significant diminution in the antidiuretic activity of the plasma. The effect of noxious stimuli was studied in rats 5 to 10 days after complete hypophysectomy. Whereas the unexposed animals had a lower titer than controls not operated on, the rats responded to noise and to pain with a marked increase in the concentration of ADS.

It is apparent from the above that neither the anterior nor posterior pituitary is essential to the release of the antidiuretic substance into the circulation. Comparison of normal, cortisone-treated 7-day adrenalectomized and hypophysectomized rats reveals that adrenalectomized rats are more sensitive than controls to the painful stimuli and that hypophysectomized rats are most sensitive. These observations are in accord with many others which reveal the increased sensitivity to noxious stimuli that occurs in the adrenalectomized and in hypophysectomized animals.

In order to establish that the observations on rats are not specific for these animals, studies were performed on man. Healthy men were given 1000 ml. of tap water, and the urine that was voided every 10 minutes was replaced with an equal volume of water in order to maintain a constant water load. When the rate of urine excretion exceeded a volume of 10 ml. per minute for two consecutive periods, a venous blood sample was drawn. Shortly thereafter the circulation through the right arm was occluded by a cuff inflated to a pressure of 180 mm. of mercury and the subject instructed to make strong gripping movements of the hand. Ischemic pain was thereby induced. At the end of 9 minutes the cuff was deflated and the subject permitted to void by the 10th minute. Ten minutes later a blood sample was drawn. A third sample of blood was

taken when the rate of urine excretion again exceeded 10 ml. per minute.

In accord with Kelsall's observations, the production of ischemic pain of the arm resulted in a marked inhibition of diuresis within 10 minutes after the cessation of pain. The duration of the antidiuresis varied from one subject to another. Minimal quantities of ADS were found in the plasma prior to the production of pain. A significant increase in the antidiuretic activity of the plasma was noted by the time maximal inhibition of water diuresis occurred. The sample drawn after the restitution of the diuresis showed a return of the plasma ADS to its pretest concentration.

The effect of noxious stimuli in man is revealed also in the observation that a surgical operation induces a marked augmentation in the antidiuretic activity of the plasma. A maximum titer was observed immediately after the operation; thereafter there was a gradual reduction, so that by two to three hours after the operation the plasma ADS titer was back to the preoperative level.

That subtler stressful situations are equally effective is suggested by studies of patients suffering from a variety of clinical disorders. Essentially two sets of values, a normal and a high set, were found in patients suffering with a variety of clinical derangements. All efforts to find some common physiological factor which could be correlated with the high values failed. The only common factor in the various clinical states which could be inferred to be related to the augmented antidiuretic activity of the plasma was the psychological reaction of the patient to the presence of his physiological derangement, i. e., to the meaning of his disease.

The aforementioned, and other, studies reveal that an antidiuretic substance is released rapidly into the circulation when the organism is exposed to a situation which has noxious significance. This antidiuretic substance behaves like the antidiuretic hormone (vasopressin). Since it is released in the absence of the hypophysis, the antidiuretic hormone must take origin in some extrahypophyseal site.

Two principal hypotheses have been proposed regarding the site of origin of the antidiuretic hormone. The commonly accepted hypothesis postulates that the ADH is secreted in the neurohypophysis and that the secretion is dependent upon the integrity of the nerve supply from the supraoptic and paraventricular nuclei. The other hypothesis attributes the secretion of the hormones of the neurohypophysis to the cells of the supraoptic and paraventricular nuclei, the neurohypophysis acting as the site of storage rather than of secretion. The latter hypothesis has been extended by Bodian, who proposed that the entire hypothalamohypophyseal pathway may be concerned in the secretory process. The data reported herein are in accord with the hypothesis that the hypothalamus is the source of the ADS secreted into the circulation in response to noxious stimuli.

DISCUSSION OF SYMPOSIUM

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THE CONTRIBUTORS of this symposium have all addressed themselves to the central mechanisms concerned with emotions, that is, to the nervous structure-functions involved in feelings. Since these mechanisms can be observed only indirectly in the intact human being, they are studied more easily in experimental animals. There immediately arises the question of the applicability of the results to the phenomena of human emotional processes, which are conscious, referred to self, and reportable. To this, I shall refer later.

Perhaps by intent, the four essayists have chosen to consider three levels of neural activity organizationally related to one another and each possessing varying degrees of integration, but all concerned with action aspects of feelings. These, then, constitute a continuum concerned in some manner with anxiety as a signal of danger, with anger or flight as a reaction to real danger, and with internal disequilibrium or disorganization from strains of various types.

Harris has demonstrated that the secretory activity of the adenohypophysis is under control of three systems of nervous innervation, including the cervical sympathetic, the parasympathetic greater petrosal branch of the seventh cranial nerve, and the hypothalamic-pituitary stalk fibers. He, however, places greatest emphasis on the portal blood supply from the pars tuberalis to the pituitary body, a link which is neurovascular. He believes that the feed-back effect to the hypothalamus occurs through the circulating adrenocortical hormones.

Mirsky, on the other hand, confirms the work of Bodian, who contends that the entire hypothalamohypophyseal pathway may be concerned in the secretory process and that the hypothalamus is the source of the antidiuretic substance secreted into the circulation in response to noxious stimuli, of which an important component is psychological stress.

Hess and Akert have shown their beautiful moving pictures demonstrating the sham rage, or pseudoaffect, arising from electric stimulation of subcortical areas. It is clear that the pseudoaffective defensive reactions resulting from stimulation resemble an angry attack, after which the animal is confused and pettable but maintains a low threshold for responses resembling anger. This stereotyped mechanism is superseded by spontaneous reactions to the threat of moving objects, among which there may be a choice of direction, that is, anger or acceptance of petting.

The physiological responses of the human neonate at birth indicate mechanisms for behavior resembling anger or fear, which many persons have considered analogous to the phenomenon of anxiety in adults. Rather, they are only the physiological prototypes for reactions to subsequent psychological events of separation and frustration. In the neonate they are central adaptive mechanisms available for later affects, but not expressing emotions at that early period, before cortical functions have matured.

It is clear from many sources of evidence that significant neural mechanisms for emotional expression are caudal to the cortex. The most cephalad structures are concerned with more complex forms of integration and greater capacity for differentiation as to type and source of response and for delay and gradation of affect. This in human beings is associated with the transcription of physiological, electrical, and chemical signs into symbols, and the attentuation of action from global emergency activity to signals of impending danger, warning of future external (fear) or internal (anxiety) disequilibrium if behavior is not modified. It is this signal effect that is so clearly demonstrated in MacLean's work on the rhinencephalon, or visceral brain. The capacity of the animal to project itself into the future (a derivative of olfaction) results in anticipatory anxiety, for

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which the noxious stimuli seemed to be concerned with quality and intensity rather than with spatial relationships.

The essayists have considered three levels of the structure-function of the central nervous system concerned with expressive or efferent activity. These form a hierarchy in terms of cephalic orientation. They may be integrated in action, and sometimes they are associated with feelings, and at other times not. Expressive activity is not necessarily connected with feelings. Certain noxious stimuli result in reflex action, since much of the stressful stimuli impinging upon the organism never reaches higher levels, against which there are barriers involving thresholds and inhibitions. Stress reactions are possible in the newborn infant before higher-level functioning and also in decorticate and decerebrate preparations. These lower-level mechanisms are, however, available to become integrated in the mechanisms concerned with true emotional states and their associated activities, involving higher-level functions simultaneously, antecedent or subsequent to stress, without reference to cause or effect. Therefore, the problems raised by Akert and others concerning the differentiation between objective or subjective does not concern the study of mechanisms. These are economically significant for the organism with or without subjective emotional states or varying degrees of consciousness.

By the same token, what is missing in this symposium is a discussion of emotions which are not synonymous with vegetative activity or central or peripheral mechanisms. There is no need to contrast the animal *versus* the human in order to consider them similar or different. We cannot anthropomorphize or project human feelings into animals or deny that they possess rudiments of feelings. Certainly, domesticated animals seem to have a narrow spectrum of feelings. The problem is simply that we cannot ascertain feelings as feelings, or even measure them crudely, except in human beings, and in them only after a certain age.

An analysis of feelings, such as fear, anxiety, anger, love, requires a consciousness, a self-reflective awareness, and a capacity for reporting information. That is why in our own work on anxiety we have insisted on free or subjectively experienced anxiety, in contrast with the so-called anxiety, which is prevented by psychologically defensive maneuvers from becoming conscious, and only apparent if these defenses are broken down, prevented by certain situations or destroyed by drugs. It is only when feelings become free that we may be informed of the subjective state and observe the physiological, biochemical, and hormonal effector mechanisms closely allied to them.

However, in our human subjects the capacity to report feelings and our ability to measure them by psychological techniques are complicated by the fact that such feelings arise in the apparent absence of external dangers or internal somatic disturbances. The afferent arc of the emotional reflex, to borrow an analogy of older neurophysiology, is not detectable by ordinary methods of observation. Furthermore, the stimulus to feelings and expressive action seems to wax and wane in some mysterious manner. How different is this from the effect of short-lasting electrical stimulation and somewhat longer afterdischarges. Nor can we attribute these emotions to build-up and eventually threshold-reaching peripheral processes, since these may be unmeasurable and announce themselves only by an explosion.

It is at this point that the cortex, which has been barely mentioned in this symposium, must be considered. Intactness of its structure-function seems necessary for subjective feelings and their variations in time. Although the visceral brain-hypothalamus-endocrine system is generally characterized by feed-back servo mechanisms and constitutes an effector black box, in a communication system, it is the cortex to which we must look for the storage, scanning, and computing of information. Herein, learning, memory, and feelings reach their richness characterizing humanness; yet current physiological knowledge helps little in elucidating these problems. It is, therefore, understandable why in spite of tremendous progress made

in studying the efferent mechanisms of emotions, little has been gained on the perceptive side, and its participation in circular activity, in the higher centers. Many people have, therefore, abandoned anatomy and physiology and utilized only psychological mechanisms extrapolated from words and other symbols.

Yet I believe much can be gained by studying cortical-subcortical relationships, as MacLean has indicated. The reciprocal change of synchronization between cortical and subcortical hippocampal discharge suggests a vast area of experimentation, which Grinker and Spiegel alluded to in their war work. As cortical activity lessened in terms of orientation of self in time and space, violent emotional feelings and active physiological discharges occurred. These quieted down as self-identifying consciousness returned. There are many other clinical phenomena indicating in the human such phasic relationships which should be studied on animals. These are not one-to-one, negative-to-positive, inhibition-to-release relationships, as our Jacksonian heritage seemed to indicate, in its dogma of levels. Even in the war studies to which I refer, subcortical activity was associated with words and complicated verbal and visual memories, along with the repetition of bodily experiences of past time.

This brings me to a final point which I should like to make concerning levels, hierarchies, and relationships. All of us like to think in mechanisms indicated by connecting straight lines. The abhorrence of discontinuities, the need for causal mechanistic chains, is evidenced by all human beings, whether the most objective physiologists or speculating psychoanalysts. Perhaps all of us in this multidisciplinary gathering could profit by abandoning a mechanistic concept, whether this be neural or humoral, and consider that the basic unit of action is a cyclic process of varying rate and extent. In so doing, we have the possibility of viewing nervous, humoral, emotional processes as composing a field.

Part or whole of each process (we should aspire to study more and more parts of each) represents nodes of activities in constant cyclic process with each other, and all parts within each process with each other. Such a transactional assumption enables us to establish a field in which all activities are affected by all others. No one part may be omitted, or any two considered in isolated reciprocal or cause-and-effect relationship. Emotions do not cause visceral expressions any more than visceral activity—they are caused by central nervous activity. The transactional processes take in as many relationships as can be defined, viewed at one time, or for which methods are available for their study. Significant is the fact that simultaneity of observation over a period of time is necessary either during observation of process in nature or during experimental manipulation of any one cycle. The relationship in time brings into consideration significant cycles especially important to the elastic, overreacting rebound phenomena moving at different rates in open biological systems.

Without going into further details, I should like to suggest that nervous, endocrinologic, and other somatic, ideational, and emotional processes can be better, and I believe more quickly, understood by transcending single systems and by discarding simple line-to-point mechanisms in multidisciplinary studies, substituting transactional studies of field processes during change and through time.

The speakers have brought a great deal to bear on problems of emotions, which are highly significant for humans because disturbance of feeling is associated with serious mental disorders and prevent our humanness from full expression. But because such studies have been made only on animals, whose feelings are not reportable, it is required that we devise methods applicable for humans by which derivative cyclic functions as close to the primary functions of the central structure-functions can be studied. As yet such derivatives are too far removed or are not subject to finer measurement, but there is progress in the air.

ELECTROENCEPHALOGRAPHIC STUDIES OF THE ENCEPHALOPATHIES

IV. Serial Studies in Meningococcic Meningitis

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and
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THE PRESENT report is the fourth in a series depicting the serial electroencephalographic (EEG) changes in the encephalopathies. Previous publications have been concerned with the chemical,[1] granulomatous [2] (tuberculosis), and viral [3] (measles) diseases of the brain.

The present study comprises a serial analysis of 50 cases of meningococcic meningitis collected over a five-year period. Clinical observations and EEG correlations were made and are recorded. The purpose of this paper is twofold: (1) to demonstrate the EEG and clinical correlation in a purulent meningitis (meningococcus) and (2) to contrast the electrocerebral alterations with that seen in tuberculous meningitis.

The principles of dynamic electroencephalography have been described elsewhere.[4] In all encephalopathies of significant severity the nonspecific response of the brain to injury is the appearance of delta activity. The persistence, evanescence, or replacement of this activity by other wave forms aids in the clinical evaluation of such syndromes.

METHODS

Electroencephalograms were taken as early as possible on patients admitted to the hospital with meningococcic meningitis. In a contagious disease of this severity it was frequently difficult to obtain initial tracings until the patient was in a less critical state. However, enough records were made early to enable a composite picture to be made. Several tracings were then taken at frequent intervals thereafter until clinical recovery occurred.

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EEG's were made on a Grass eight-channel ink-writing oscillograph. A minimum of thirteen 27-gauge needle electrodes were inserted into the scalp and ear lobes, with the use of bipolar as well as monopolar leads (with an average reference or one on each ear or on the cortex).

CLINICAL DATA

Criteria for Diagnosis.—All 50 cases had a purulent spinal fluid with over 60% polymorphonuclear cells (Tables 1 and 2). The average number of white blood cells per cubic millimeter was 9000. Smears demonstrating gram-negative diplococci in the spinal fluid or positive cultures were noted in 46 cases. The remaining four were considered to have meningococcic meningitis on the basis of purulent spinal fluid, presence of petechiae,[5] and rapid recovery under therapy, despite inability to demonstrate the organism.

Ages.—There were 40 patients under the age of 16 and 10 above. The age range was from six months to 54 years. Twenty-eight of the group were under 5 years of age.

Sex.—There were 25 males and 25 females.

Incidence of Petechiae.—Petechiae were seen in 40 patients, or 80%.

Therapy.—All subjects received sulfadiazine and penicillin during their illness. The patients who seemed to be developing the Waterhouse-Friderichsen syndrome received, in addition, either adrenocortical extract or corticotropin (ACTH).

Duration of Illness.—Morbidity averaged 10.5 days.

Duration of Life.—None of the patients in this series succumbed to meningococcic meningitis. The usual mortality rate in previously reported series is 3% to 6%.[6] Eighty-three cases of meningococcic meningitis were seen at Louisville General Hospital for the five-year period 1948-1952. The mortality rate was 9.6%.

TABLE 1.—*Clinical and Laboratory Findings in Fifty Cases of Meningococcic Meningitis*

Case	Patient	Age, Yr.	Race	Sex	Petechiae	Days of Illness	Initial CSF * (WBC's)	No. of EEG's
1	SC	4	W	M	+	7	5,080	1
2	AS	17	W	F	+	12	8,750	3
3	JM	½	N	M	+	6	8,250	1
4	EC	4	W	F	+	4	15,500	1
5	AL	28	W	F	+	8	5,000	6
6	TS	3	W	M	+	6	7,500	1
7	WK	3½	W	F	+	7	3,650	1
8	MS	½	W	F	+	10	2,020	1
9	JR	6	N	M	0	14	7,250	7
10	VK	23	W	F	0	11	1,410	2
11	JS	9	W	F	+	9	9,650	6
12	PA	15	W	M	+	8	11,000	6
13	OB	2½	W	F	+	5	13,000	1
14	RB	3½	W	M	+	34 † ‡	3,388	1
15	SF	32	W	M	+	13 †	14,500	4
16	GW	4	W	M	0	8	7,800	2
17	SP	3½	W	F	+	8	9,750	4
18	LG	30	N	F	0	14 †	12,800	4
19	JE	½	N	M	0	8	6,440	1
20	AP	4	W	M	+	13	17,000	4
21	JH	2½	W	M	0	6 †	14,000	2
22	SS	1	W	F	+	6	1,060	1
23	SO	1	W	F	+	15	2,358	2
24	MR	4	W	F	+	12	1,000	1
25	JH	½	W	F	+	8	11,000	2
26	EF	40	N	M	+	13	8,400	6
27	EA	1	W	F	+	6	5,970	1
28	JM	12	W	F	+	10	3,880	1
29	CH	10	W	M	+	7 †	44,650	3
30	JB	54	W	M	0	20 †	50,000	4
31	LE	2	W	F	+	6	3,500	1
32	LL	4	W	M	+	16 ‡	Not done	2
33	FH	22	W	F	+	10	25,000	3
34	EB	12	W	F	+	4	7,800	5
35	WK	16	W	M	+	6	9,000	1
36	FD	3½	W	M	+	6	13,500	3
37	PR	2	W	F	+	8	4,160	2
38	GW	3	N	M	0	27 ‡	2,640	4
39	BH	15	W	M	+	5	9,950	1
40	CL	1	W	F	+	7	11,250	1
41	JH	10	W	M	+	18 ‡	14,900	3
42	JS	½	W	M	0	14 †	1,900	1
43	JB	1½	N	M	+	10 †	5,640	2
44	RW	13	W	M	+	7	4,160	6
45	EC	43	N	F	+	6 †	1,200	4
46	WB	13	W	M	0	7	4,600	1
47	VD	1	W	F	+	9 †	6,150	5
48	EB	9	W	F	+	7	220	2
49	JK	½	W	M	+	17 †	3,360	2
50	BW	11	W	F	+	12	12,800	1

There were no deaths in this series. All patients received penicillin and sulfadiazine.
* CSF indicates cerebrospinal fluid; †, seizures during illness; ‡, Waterhouse-Friderichsen syndrome; W, white; N, Negro; M, male; F, female.

TABLE 2.—*Summary of Fifty Cases of Meningococcic Meningitis*

Ages	40 children and 10 adults
Sex	25 males and 25 females
CSF	Average number WBC's/cu. mm. was 9,000; over 60% polymorphonuclear cells. 92% (46 cases) had positive smear and/or culture for Meningococcus. The remaining 4 cases had purulent CSF, petechiae, and rapid recovery with therapy
Petechiae	80% (40 patients) had petechiae
Duration of illness	Average 10½ days
Mortality	No deaths
Complications	Hearing loss, 3; behavior disturbance, 1; septic skin infarcts, 1
Waterhouse-Friderichsen syndrome	4 cases
Treatment	Penicillin and sulfadiazine; adrenocortical extracts or corticotropin used for Waterhouse-Friderichsen syndrome
EEG's	131; of these, 30 had 2 or more EEG's, and 20 had 3 or more EEG's

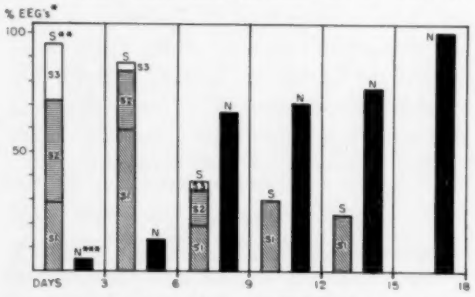

Fig. 1.—Analysis of serial EEG changes in 50 cases of meningococcic meningitis.

It is to be noted that EEG recovery began in the first week of illness, as indicated by the sharp drop in the slow (*S*) activity. Definite clinical improvement in this series occurred by the 5th day, preceding the delta resolution, which started by the 6th to the 9th day and was usually complete by the 14th day.

* indicates per cent of normal and abnormal EEG's for each three-day period. ** *S* indicates slow activity: S_3, severely slow (½ to 2½ cps); S_2, moderately slow, and S_1, minimally slow.

*** *N* indicates normal or fast activity.

Complications.—Three patients had moderate impairment of hearing following recovery from meningococcic meningitis. The defect was bilateral in two patients and unilateral in one. One adult exhibited childish behavior and mild confusion during convalescence. A history of chronic alcoholism was considered contributory to his abnormal behavior. In one infant, aged 1½ years, septic infarcts to both feet required skin grafting.

There were four cases of Waterhouse-Friderichsen syndrome, as manifested by rapid progression of symptomatology, peripheral vascular collapse, and fulminating purpura.

Grand mal seizures occurred in 11 cases either as an initial manifestation or during the course of the disease. An incidence of 22% would seem significant, particularly since only one patient in the group gave a history of previous seizures.

Electroencephalograms.—A total of 131 EEG's were made, with an average of 2.6 per patient. Rapid clinical recovery and early discharge from the hospital limited the number of EEG's made. The clinical course was adequately reflected, however, by short serial study. The initial EEG was made, on an average, on the sixth day. Records on 12 patients were made initially within the first 48 hours of illness.

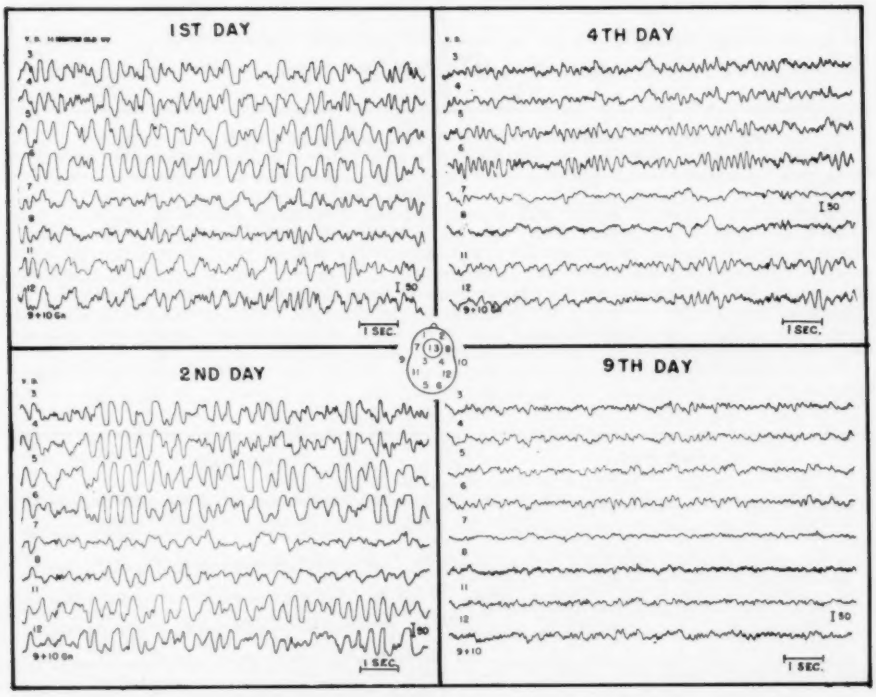

Fig. 2.—Uncomplicated case of meningococcic meningitis in 14-month-old infant.

V. D. had abrupt onset of fever, lethargy, and vomiting. On admission the temperature was 104 F (rectal), the neck was stiff, and there was a generalized purpura. Spinal fluid showed 6150 white blood cells, predominantly polymorphonuclear leucocytes. EEG made on first hospital day, simultaneous with initiation of therapy, showed diffuse high-voltage two to four per-second waves. Eighteen hours later the EEG was still diffusely slow, though clinically the child was improved. On the fourth day the patient had become afebrile and was eating well, and the neck was only mildly stiff. EEG on this day showed only an occasional delta wave, with much faster and more stable background activity. By the ninth day the patient was asymptomatic. The tracing on this day was essentially normal.

Note rapid normalization of the EEG between the second and ninth days and compare with that seen in Figure 3.

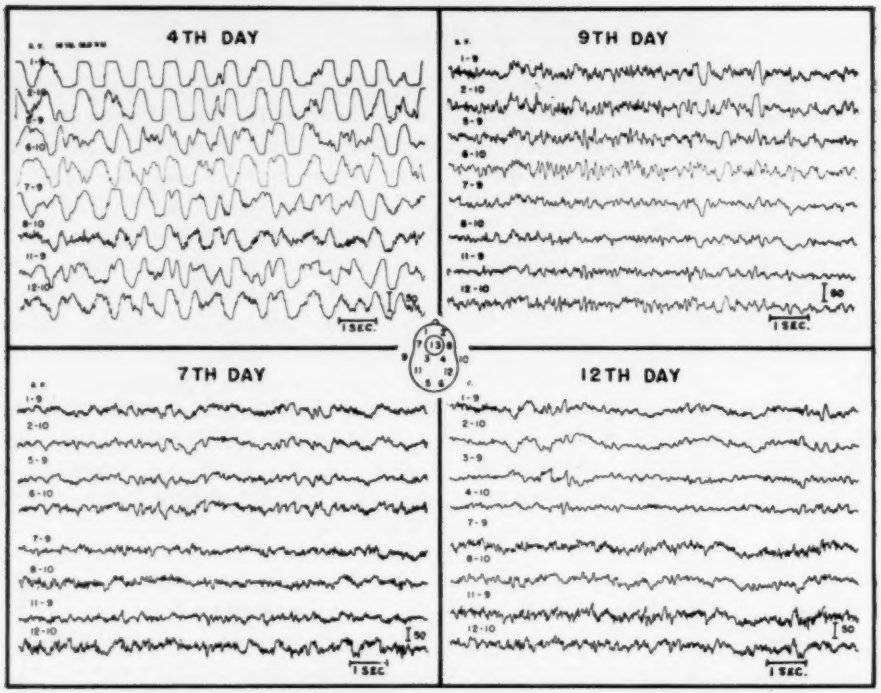

Fig. 3.—An uncomplicated case of meningococcic meningitis in an adult.

S. F., a 32-year-old man, had sudden onset of headache, fever, and convulsions. On admission there was noted stupor, neck stiffness, petechiae, right hemiparesis, and temperature of 101 F (rectal). Spinal fluid showed 14,500 white blood cells. By the fourth hospital day he had only moderate stiffness of neck, but he was drowsy and had intermittent periods of confusion. The right hemiparesis was clearing. EEG on this day showed continuous high-voltage one- to three-per-second activity in all areas. By the seventh day the patient was rational, the neck was only slightly stiff, and only minimal paroxysmal slow activity was seen. By the ninth day he was eating well, the temperature was normal, and there were no further confusional episodes. The record on this day showed a moderate amount of electrical seizure activity, with no delta waves. The EEG on the 12th day, at which time he was ambulatory and asymptomatic except for diminished hearing on the right side, was generally dysrhythmic.

Note the rapid changes toward normal between the fourth to seventh days and the similarities between this adult record and that of an infant (Fig. 2).

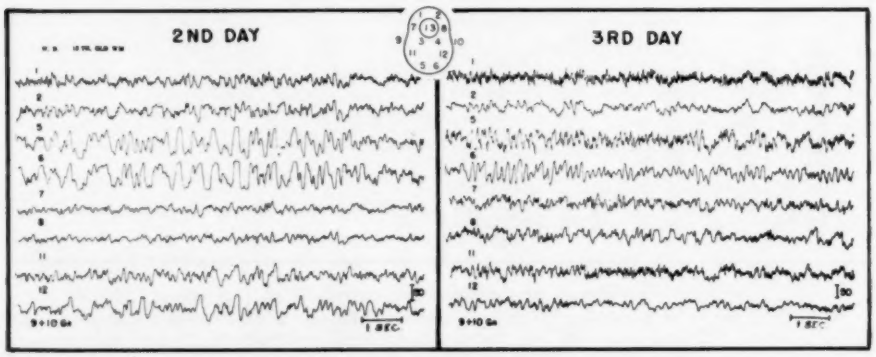

Fig. 4.—Occipital slowing in meningococcic meningitis.

W. B., 13-year-old white boy, acutely developed fever, headache, and lethargy. On admission the temperature was 105 F (rectal) and the neck was stiff. No petechiae were seen. Spinal fluid showed 6300 white blood cells. By the second day the patient was more alert and the neck was less stiff. EEG showed high-voltage three- to four-per-second waves predominantly in the occipital and posterior temporal areas. On the third day he was much improved, was eating, and was complaining only of mild headache. The EEG showed only an occasional random slow wave.

Note the focal slow activity in the posterior regions. The significance of this frequently occurring phenomenon is not known.

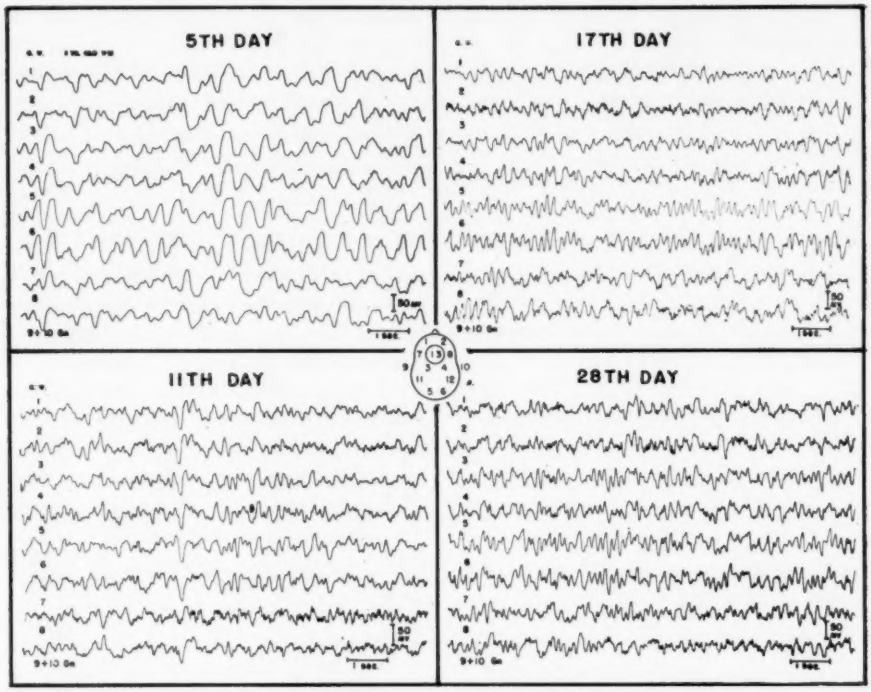

Fig. 5.—Meningococcic meningitis complicated by Waterhouse-Friderichsen syndrome.

G. W., 3-year-old white boy, had abrupt onset of fever, vomiting, and lethargy. At time of admission he was critically ill, and unconscious; temperature was 103 F (rectal), the neck was rigid, and the blood pressure was unobtainable. Spinal fluid contained 2640 white blood cells. The patient responded slowly to adrenocortical extract, penicillin, and sulfadiazine. On the fifth day he was still drowsy, the neck was very stiff, and the temperature was falling. The EEG showed diffuse high-voltage two- to three-per-second waves. On the 11th day he was more alert, the neck was mildly stiff, temperature was normal, and he was beginning to eat well. The record was much faster, but still showed a moderate amount of delta activity. By the 17th day he was alert, and there were no focal neurological signs. The EEG showed much faster background activity but random slow waves are still present. On the 28th day, when he was ambulatory and asymptomatic, the EEG showed faster background activity and some slow spike discharges.

In comparison to Figures 2, 3, and 4, note the prolonged period for delta recovery which in this case did not occur completely until the 28th day of illness. Records such as these were not encountered in uncomplicated meningococcic meningitis.

RESULTS

Brain damage or dysfunction was estimated by the degree and duration of delta (slow) activity. In Figure 1 the results of this grading are tabulated for the whole series. Slow activity was estimated on the following scale: S_3, diffusely slow with average frequency of less than three per second; S_2, paroxysmally slow or less than six per second, and S_1, minimal slow activity. Grading was done on the basis of each patient's series. Corrections were made for age. However, total change in each series was the main comparative point. A normal EEG or a record which showed a dysrhythmia other than that of slow activity was labeled normal (N).

In Figure 1 it is noted that EEG recovery begins in the first week of illness, as indicated by the sharp drop in the slow (S) activity. Definite clinical improvement occurred about the fifth day (4.6 days). This was earlier than the delta resolution, which began between 6 and 9 days and was complete between the 13th and 14th days. In other words electrocerebral improvement lagged two to three days behind the clinical course.

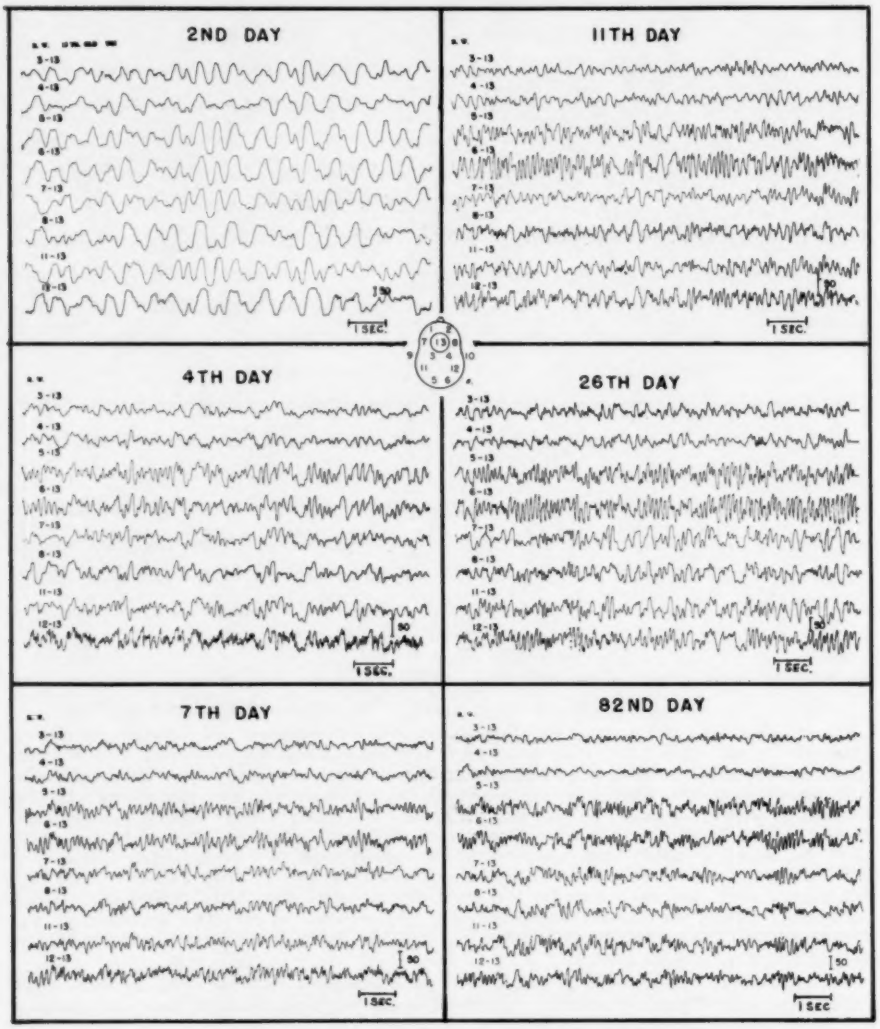

Fig. 6.—A case of meningococcic meningitis, followed by serial EEG for three months after onset of illness.

R. W., age 13 years, developed acute nausea, vomiting, fever, and headache. On admission the temperature was 104 F (rectal). He was in stupor, had a very stiff neck, and demonstrated generalized petechiae. The initial spinal fluid showed 4160 white blood cells. On the second day he was rational and was able to take food. His neck was still very stiff and headache was a constant complaint. The EEG on this day showed obliteration of all normal frequencies by continuous high-voltage two- to three-per-second waves, more marked in the right posterior area. By the fourth day the petechiae were gone and he was alert and rational.

The recording shows a fair background frequency of eight per second with only a moderate amount of delta activity. On the seventh day, when he was afebrile, the EEG showed only minimal slowing, which was most evident in the temporal areas. On the 11th day the tracing demonstrated faster background activity, with frequent slow-spike discharges. No delta activity is apparent and the record is becoming dysrhythmic. The EEG on the 26th day was similar to the previous record except that the spike-wave patterns are now more pronounced in the left temporal region. The record on the 82d day was less dysrhythmic.

The above demonstrates the gamut of long-term changes in the EEG in meningococcic meningitis: initial marked slow activity, rapid delta resolution, replacement by seizure discharges, then normalization or permanent dysrhythmia.

The rapid EEG recovery is demonstrated in Figure 2, a case of an infant with uncomplicated meningococcic meningitis. Figure 3 shows that the EEG course is very similar in adults. These two cases are representative of the bulk of material in this series.

In many instances, particularly children, the slow activity, though diffuse, was maximally present in the occipital and posterior temporal regions. Its significance is not known, but one other investigator described such changes in a single case report.[7] Figure 4 shows occipital slowing in an uncomplicated case of meningococcic meningitis.

In four cases of Waterhouse-Friderichsen syndrome the delta resolution was delayed into the second week of illness. Figure 5 demonstrates this delay. Figure 6 illustrates a long-term (three months) follow-up.

Chronic meningococcic meningitis was not encountered in this series.

COMMENT

In meningococcic meningitis the EEG is, initially, moderately to severely slow. The slow activity is more apparent in children than in adults, but the degree of slowing, when compared with the basic normal rhythm for each patient's age, was the same. From an EEG standpoint meningococcic meningitis produces an encephalopathy of equal severity in adults and children.

At the onset and during the early stages of meningococcic meningitis the slow activity is usually diffuse, but maximal in the occipital and posterior temporal areas. After specific treatment is started, the resolution of delta activity is markedly accelerated. During this evolution a large amount of electrical seizure or fast activity displaces the delta waves. Finally, the dysrhythmia merges into a relatively normal pattern.

The entire stage of resolution is very short and is one of the most striking features of the electroencephalogram. Even in the severest form of the disease, namely the Waterhouse-Friderichsen syndrome, delta activity begins to clear within one week and has completely resolved by the 14th day of illness.

In a few cases in which the meningococcus could not be demonstrated, the brief EEG recovery period seemed to add weight to the clinical diagnosis of meningococcic meningitis. Experience with the EEG in the pneumococcic and influenzal meningitides suggests that these purulent infections take longer than one to three weeks for delta activity to resolve.* In tuberculous meningitis delta resolution requires weeks to months to clear, even in cases with a favorable outcome.[2]

Thus, in meningococcic meningitis delta persistence or delayed resolution beyond a two-week period would strongly suggest an error in diagnosis or herald a complication. Parenthetically, it would appear injudicious to discontinue antibiotic or sulfonamide therapy in the face of persistent delta activity at any time in the illness, despite a normal clinical picture.

Almost one-fourth of the subjects in this series had seizures of a convulsive nature, occurring usually at the onset of the illness.

SUMMARY

Fifty cases of meningococcic meningitis were studied by correlating serial EEG's with clinical observations (Table 2). Forty children and 10 adults were included. The number of EEG's per patient ranged from one to seven and averaged 2.6 per case.

Initial EEG's were diffusely slow, with maximal delta (slow) activity seen frequently in the occipital and posterior temporal regions. The clinical and EEG course was similar in adults and children.

Most striking was the rapid normalization of the EEG under therapy, which occurred in the first six to nine days. This rapid recovery of electrocerebral function would give added weight to the diagnosis of meningococcic meningitis because it is not usually seen in the other purulent meningitides.

Prolongation of EEG recovery beyond a two-week period would indicate other etiologic factors or might point to complications.

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News and Comment

GENERAL NEWS

Centennial of Saint Elizabeths Hospital.—On Jan. 15, 1855, Saint Elizabeths Hospital, in Washington, D. C., admitted its first patients. This year it celebrates its centennial. Now a component unit of the U. S. Department of Health, Education, and Welfare, it was established by Act of Congress as the Government Hospital for the Insane. Dorothea Lynde Dix (1802-1887), one of the most remarkable women America has produced, was responsible for this action by the Congress, and her name will be given this year to the new 420-bed Admission and Treatment Building at Saint Elizabeths, the Dorothea Lynde Dix Memorial Pavilion.

On May 5 and 6, 1955, there will be held at the Hospital a two-day meeting, with invited guest speakers of international repute. An historical pageant depicting the life and works of Miss Dix—planned, written, and enacted by patients of the Hospital—will also be presented at this time.

During its hundred years of service, this Hospital has had but five superintendents, including the present Superintendent, Dr. Winfred Overholser. All five have been presidents of the American Psychiatric Association. Throughout its existence, Saint Elizabeths has been respected both in this country and abroad as a public mental hospital of the highest repute. Never indentified with any single school of psychiatric thought, it has been proud of its eclectic approach to the treatment of the mentally ill. It has trained thousands of psychiatrists, psychologists, psychiatric nurses and social workers, ministers, occupational therapists, and others engaged in the treatment of the mentally ill.

In the twentieth century, Saint Elizabeths has been noted for its pioneering efforts in establishing neuropathology and clinical psychology departments. It was the first hospital in the Americas to use the malaria treatment for dementia paralytica. Its late superintendent, Dr. William A. White, was one of the few American psychiatrists to give early support to the then new psychoanalysis of Freud. Together with Jelliffe, he founded (in 1913) the first psychoanalytic journal in America. Dr. Edward J. Kempf, of the staff of Saint Elizabeths Hospital, was probably the first American psychiatrist to treat schizophrenia in an American hospital by the psychoanalytic technique. His early book on psychopathology was one of the first in America to present a psychopathology that was psychologic in its premises.

The late Harry Stack Sullivan carried out his earliest work in psychiatry at Saint Elizabeths. Several of Korzybski's early studies in semantics were conducted here. The several superintendents, notably Drs. White and Overholser, as well as a number of members of the staff (Bernard Glueck, John Lind, Ben Karpman), have enjoyed outstanding reputations as forensic psychiatrists.

Shortly after the Russo-Japanese War, military psychiatry was introduced to this country at Saint Elizabeths Hospital and, during the past forty years, there has been a close liaison between the psychiatric division of the military medical services and the Hospital. In World War II, hundreds of medical officers, nurses, corpsmen, and Red Cross workers received their psychiatric orientation here.

Psychodrama was first adopted for use in a public mental hospital at Saint Elizabeths, and the arts, including music and the dance, have been developed here as valuable therapeutic tools.

The only public mental hospital in America which offers an A. M. A.-approved general internship is Saint Elizabeths.

The annals of this Hospital, the only one of its kind in America, proudly record a hundred years of Progress in American Psychiatry.

AMINO ACIDS OF THE CEREBROSPINAL FLUID

Normal Paper Chromatographic Pattern and Its Duplication in Multiple Sclerosis

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and
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ALTERATIONS in the proteins * of the cerebrospinal fluid (CSF), and in the cell count and the colloidal reactions,[4] occur in an appreciable proportion of patients with multiple sclerosis. Observation of these changes has proved to have some diagnostic importance, although normal findings in the CSF often enhance the probabilities in favor of multiple sclerosis in differential diagnosis.[5] There are also reports † of statistically significant alterations in plasma proteins associated with this disease.

The present study deals with the free amino acids of the CSF and was undertaken with the thought that qualitative or quantitative changes might be found which would be of value in the diagnosis of multiple sclerosis or in explaining its cause or causes. This expectation was not realized, but new information has been obtained concerning the free amino acids of the normal CSF and changes observed in neurological disorders other than multiple sclerosis.

The first reported investigation of the free amino acids of the CSF would appear to be the one published by Solomon, Hier, and Bergeim,[9] who utilized a microbiological method for the assay of arginine, histidine, isoleucine, leucine, lysine, phenylalanine, threonine, valine, tyrosine, methionine, and cystine. Harris [10] had earlier reported specific glutamine analyses of the CSF and found that this amino acid alone accounted for approximately 70% of CSF free amino nitrogen. Richter, Dawson, and Rees [11] reported values of 6.9 to 8.6 mg. of glutamine per 100 ml. of CSF.

Boulanger and Biserte [12] utilized paper chromatography in the identification of amino acids both in blood plasma and in CSF. They used a desalting procedure which involved vacuum drying and extraction with acidified acetone, and identified aspartic acid, glutamic acid, serine, aminoacetic acid (glycine), alanine, valine, leucine, and traces of diamino acids in the CSF.

Pond [13] examined, by paper chromatography, CSF specimens from 121 patients with mental disease, the majority being cases of manic-depressive psychosis or of schizophrenia. Glutamine, alanine, valine, leucine (including isoleucine), aminoacetic acid, and glutamic acid were identified.

Kemali and Porcellati [14] reported the presence of glutamic acid, aspartic acid, and possibly serine in the CSF of subjects with neurological disorders. They also found that in the CSF of normal subjects free aminoacetic acid, alanine, and valine were present in concentrations approximating 2.0, 1.8, and 1.7 mg. per 100 ml., respectively. They did not report any value for glutamine.

Ludewig [15] studied a group of subjects with a variety of neurological disorders and found the mean glutamine content of the CSF to be 7.35 mg., with a standard deviation of 2.0 mg., per 100 ml. of CSF. He found no relation between glutamine concentration and the type of disorder. This same worker also reported glutamic acid to be present in traces only, or not at all, and did not find any evidence for the presence of γ-aminobutyric acid.

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This study was supported by a grant from the National Multiple Sclerosis Society.

* References 1, 2, and 3.

† References 6, 7, and 8.

Walshe [16] found glutamic acid, aminoacetic acid, serine, alpha-alanine, glutamine, valine, and leucine or isoleucine or both to be present in the CSF. Using a very approximate quantitative method, this investigator found these amino acids to be present in concentrations of 0 to 3, 0 to 3, 0 to 6, 0 to 6, 0 to 21, 0 to 3, and 0 to 6γ per milliliter of CSF, respectively. The values given by this investigator for aminoacetic acid, alanine, and valine are considerably below the values given by Kemali and Porcellati for the same acids, even after allowance is made for the fact that a visual comparison method was used by Walshe for quantitation. Gilligan, Moor, and Warren [17] found a spot which corresponded to γ-aminobutyric acid in the single CSF which they investigated. This particular amino acid is present in appreciable concentrations (32γ to 103γ per gram of fresh tissue) in the brain,[18] but only in minute amounts elsewhere in the animal body. Although formed by alpha-decarboxylation of glutamic acid,[19] the most interesting reaction of this substance is its transamination with α-ketoglutaric acid, with the formation of succinic semialdehyde.‡

Schönenberg [22] has reported the presence of lysine, alanine, and leucine (or isoleucine or both) in unhydrolyzed CSF. The same amino acids were found in hydrolyzed specimens, plus glutamic acid, aminoacetic acid (or serine or both), cystine, and valine (or methionine or both).

Aqueous humor of rabbits [23] has been found to contain the same amino acids as the blood serum of the same species, and in similar amounts. These data have been interpreted to mean that free amino acids enter the aqueous humor by diffusion.

EXPERIMENTAL STUDY

The method of paper chromatography was selected on account of its usefulness in the separation of a large number of constituents reacting very similarly to more classic analytical procedures. The theory of this process of separation is still a matter of dispute,§ but the practical requisites for a reliable analytical technique have been well worked out.[26] A report of our earlier studies, not including any fluids from multiple sclerosis patients, has been published.[27]

The equipment used in the paper chromatographic study of the free amino acids of the CSF was as described in our previous report with the following exceptions:

Chromatography tanks: These tanks were constructed from stainless steel and plate glass. They measure 28 in. (71 cm.) in width, 25 in. (63.5 cm.) in height, and 18 in. (45.5 cm.) in depth. The joints were sealed with a compound used by builders of aquaria, this being followed by a coating of paraffin, which was brushed on. A suitable rack, adjustable for height, from which to suspend the papers was fabricated from stainless steel. For each tank suitable troughs and trays were procured of materials that were resistant to the solvents used in developing the chromatograms. Glass rods cut to size were used to suspend the papers in the tanks. Stainless steel clips were used to secure the papers to the glass rods. The tanks were covered with single pieces of plate glass, and petrolatum U. S. P. was used to make an airtight seal.

Micropipettes in 2, 5, and 25μl sizes were used in spotting the papers with the samples. A commercial model spray gun was eventually adopted, although home-made atomizers were successfully used.

Solvent mixtures, reagents, and solutions used in this study include the following:

Propanol-Water Mixture.—Eighty parts of *n*-propanol to 20 parts of distilled water is used in the first dimension, and is made up fresh each time.

Butanol-Acetic Acid-Water Mixture. — Two hundred fifty parts of *n*-butanol is mixed with 250 parts of water. To this, 60 parts of glacial acetic acid is added. After mixing the solvents are allowed to separate. The lower layer is discarded and the upper layer used. This solvent also can be used in

‡ References 20 and 21.

§ References 24 and 25.

the first dimension. It must be made fresh each time it is used.

Phenol-Water Mixture.—Eighty parts of phenol (Merck reagent grade) is diluted with 20 parts of distilled water. To this is added 8-hydroxyquinoline to give a concentration of 0.08% (w/v). This solvent is used in the second dimension.

Ninhydrin Spray Solution.—This is a 0.2% solution (w/v) of ninhydrin in a *n*-propanol-water mixture (90:10).

Silver Nitrate Reagent.—This is a solution containing 1 gm. of silver nitrate per 100 ml. of water.

Standard Solution of Amino Acids.—A mixture of the commonly expected amino acids is made up by dissolving 0.001 mole of each amino acid in 100 ml. of N HCl to give a concentration of 0.01 mole per liter. Included in this mixture are aspartic acid, glutamic acid, serine, aminoacetic acid, threonine, glutamine, alpha-alanine, tyrosine, lysine, histidine, arginine, γ-aminobutyric acid, tryptophan, valine, phenylalanine, and leucine. Before running a chromatogram with this mixture, we neutralize the spot by exposure to ammonia vapors for approximately 30 seconds.

Preparation of Cerebrospinal Fluid for Chromatography.—As soon as possible after a sample of CSF is obtained, it is cooled to —20 C and kept there until used. This procedure was followed with all fluids except those which were shipped by postal carrier. These latter fluids were preserved with ethanol, as described in the paragraphs immediately following.

In preparation of the fluids for chromatography, they are first allowed to defrost at room temperature. After thorough mixing, a measured amount (usually 2 to 4 ml. of CSF) is pipetted into a 50 ml. centrifuge tube. Ten volumes of 95% ethanol is added for every milliliter of CSF used. The precipitated protein is spun down in the centrifuge for 10 minutes at 600 g. The supernate is decanted into a Pyrex evaporating dish and brought to dryness on a steam bath.

The dried material is taken up in approximately 15 ml. of distilled water in several portions, which are combined and decanted into the desalting apparatus.[28] With a potential difference of about 60 volts, desalting is completed in about 20 minutes, when the current reaches a value of 150 ma. A negative test for chloride ion with 1% silver nitrate is considered sufficient evidence that most salts have been removed.

After desalting, the fluid is concentrated to a volume of about 0.25 ml. by pipetting the desalted fluid into a 50 ml. tapered Pyrex centrifuge tube and blowing a jet of washed air over the surface of the fluid in the tube, which is kept warm by a steam bath. The slight condensation occurring on the inside of the tube serves to wash down the sides of the tube. When the volume is reduced to about 0.25 ml., the fluid is ready for spotting. In spotting, the size of the spot is kept as small as possible.

Certain specific precautions should be observed in preparing the CSF for chromatography. Precipitation of protein with at least 10 volumes of 95% ethanol is necessary. Desalting must be halted as soon as a test for chloride ion is negative or when the current reaches 150 ma. Errors derived from the desalting procedure will be discussed later. Finally, in concentrating the fluid for spotting, care must be taken not to allow the contents of the tube to go to dryness. If concentration to dryness is inadvertently obtained, thorough rinsing of the tube is necessary to remove all deposited material.

Chromatographic Procedure.—Separation of the amino acids is accomplished by ascending two-dimensional paper chromatography. The concentrated CSF is applied to the paper by using a capillary with a finely drawn tip. Calibrated micropipettes are used for delivering standard solutions onto the paper.

The spot is applied approximately 3 cm. from one edge of the paper and 5 cm. from the other edge. The 3 cm. edge is in the long direction of the paper, and this edge is set into the propanol solvent for the first dimension. The solvent is allowed to climb over-

night (about 18 hours). The solvent must be freshly prepared. The paper is removed from the tank after the overnight run; the solvent front is marked, and the paper is dried in air. The excess paper is cut off about 4 cm. behind the solvent front. The paper is then refolded in the second dimension and suspended in the phenol solvent, which should be changed every run. A few drops of concentrated ammonia water are added to the tank just before closing it. This assures proper migration of the basic amino acids. The solvent is allowed to climb overnight (about 18 hours).

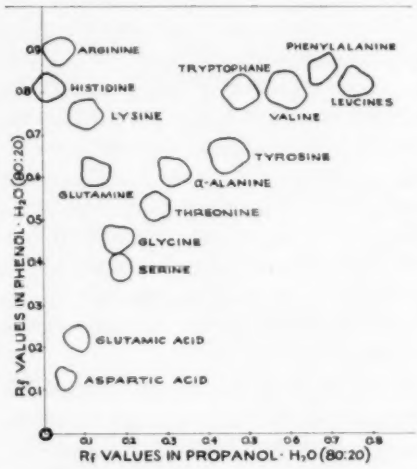
After the phenol run, the paper is dried overnight in air, an exhaust fan being used to remove the vapers. The paper is then evenly sprayed with 0.2% ninhydrin solution, and full color development takes place overnight with the paper hung at room temperature.

Factors Affecting Separation of Amino Acids.—It is commonly known that high concentrations of inorganic salts will interfere with the proper development of chromatograms of amino acids. It is probably less well known that high concentrations of sugars (in this particular study, the glucose of the concentrated CSF) have a similar effect on amino acids. This effect was noticeable whenever the butanol-acetic acid solvent mixture was used. By use of *n*-propanol as the solvent, this effect was minimized, since glucose migrates faster than the amino acids, with which it would otherwise interfere.

As a matter of interest, the result of centrifugal ultrafiltration of the CSF was studied. The resulting ultrafiltrate was found to be protein-free, but this procedure did not in any way improve the separation of the amino acids.

Use of a Synthetic Cerebrospinal Fluid.—In initiating the studies on the free amino acids of the CSF, it was decided to treat a standard mixture of amino acids as a synthetic spinal fluid. This mixture has already been described in the list of solvents and reagents. The resulting separation of the mixture of amino acids served as a guide to the identification of most of the amino acids found in the CSF. Repeated runs with this mixture gave a reliable pattern of separation, which is shown in the accompanying Figure. Results such as those depicted in this Figure were not so clearly obtained with the desalted spinal fluids, nor were they obtained when desalted standard solutions were run.

Losses During Preparation of Cerebrospinal Fluid for Chromatography and During Chromatographic Development by the Solvent Systems.—The various steps and manipulations involved in preparation of a CSF for chromatography introduce possible sources of loss. Each such source can be checked individually, and usually a negligible



Distribution pattern of amino acids in synthetic cerebrospinal fluid.

amount of loss is detected, with the exception of the losses incurred during the desalting procedure. From the nature of the experiment, it becomes prohibitive to follow the losses in a step-by-step fashion; rather, one must rely on an over-all estimate. To obtain this estimate, a series of synthetic fluids were made up in isotonic saline solution. Each such sample contained 0.05μM of each amino acid to be studied and was diluted to 15 ml. with distilled water. Next, the solution was desalted in the same manner as the actual fluids. As soon as desalting was completed, the synthetic CSF was removed and concentrated to about 0.25 ml. and spotted onto

filter paper for chromatography. The experimental and control chromatograms were run in the same tank at the same time. A series of 12 such experiments was run (Table 1). From these, an average loss for each amino acid was computed, and this loss was corrected for in the final results. It will be noted that no results are listed for losses incurred on arginine or lysine. This omission acknowledges the fact that the procedure is very unsatisfactory for these amino acids. The effect of desalting on arginine has been noted by other workers, in particular, Stein and Moore.[29] Arginine may undergo as much as an 80% loss during the desalting process. Histidine may also be lost, and clear-cut spots do not always result with this amino acid after desalting is completed. Lysine was recovered by Stein and Moore in percentages between 86 and 99, but our losses of this amino acid were of greater magnitude. The ion exchange method of desalting [30] also involves serious losses of arginine and lysine.

TABLE 1.—*Percentage Recovery of Amino Acid from Desalted Synthetic Cerebrospinal Fluid by Photometric Quantitation*

Sample No.	Aspartic Acid	Glutamic Acid	Serine	Aminoacetic Acid	Threonine	Glutamine	Alanine	Tyrosine	Histidine	Valine	Phenylalanine	Leucine
1	95	93	84	96	95	0	95	53	0	48	54	68
2	100	78	123	110	55	63	73	27	39	59	66	0
3	125	93	105	90	58	76	73	25	54	70	92	63
4	143	104	84	87	51	59	57	41	0	70	76	93
5	146	95	86	83	58	55	45	28	28	55	20	71
6	100	..	104	118	..	83	54	62	..	68	74	..
7	117	..	118	138	55	81	83	61	..	73	67	76
8	153	104	98	138	26	52	62	33	..	67	47	..
9	97	..	78	110	23	..	40	62	40	57	38	..
10	90	..	70	159	32	47	77	88	36	76	47	69
11	98	..	92	80	40	54	61	62	34	71	44	34
12	180	100	133	155	36	20	36	23	..	65	39	54
Mean	120.3	95.3	97.9	113.7	48.1	53.6	63.0	47.1	28.9	64.9	55.3	58.7
S. D.*	29.0	9.0	19.3	28.0	20.2	25.1	13.2	20.5	19.3	8.4	20.1	27.2
S. E.†	8.4	3.4	5.6	8.1	6.1	7.6	3.8	5.9	6.8	2.4	5.8	9.1

* Standard deviation.
† Standard error.

Method for Quantitation of Amino Acids.—The spot diameter-absorbance method was used for quantitation in this study. A similar technique has been utilized by many workers.‖

The instrument used is a Photovolt electronic densitometer (Model 525). The instrument consists of two units; one is a search unit outfitted with a photoelectric cell; the other is an amplifier which records relative gain in terms of absorbance units. The spots developed with ninhydrin as described are outlined and their diameters measured. Valine, phenylalanine, and leucine usually give elongated spots. For these the short dimension is measured and used.

After the spot size is determined, the absorbance of the center of each spot is measured. An area of paper adjacent to the spot is used as a blank for setting the machine to zero. Multiplying spot diameter by the spot density gives an arbitrary value (diameter × absorbance), which in the case of control papers is plotted against the amount of amino acid used. In the present work standard curves were obtained by running control chromatograms in duplicate. A straight-line relationship is obtained for most amino acids in the range of concentrations used. However, the lines often do not intersect the origin of the axes, and readings below the 0.01 μM level are only approximate in such cases. From the standard curves one can read off the amount of amino acid in an un-

‖ References 31 through 34.

known spot by determining the diameter × absorbance of the spot and referring to the standard curve for that particular acid. The reliability of this method for the individual amino acid is indicated by the data in Table 1.

For the amino acid glutamine, direct application of this technique does not yield reliable results, and special handling of this amino acid is necessary. In all the fluids studied glutamine was consistently found to represent the major portion of the amino nitrogen present. Quantitation by the method just described led to constant, but low, values for the glutamine content in the CSF.

TABLE 2.—*Direct Chemical Analysis of Cerebrospinal Fluid for Glutamine, As Compared with Photometry of Paper Chromatograms*

	Glutamine, Mg./100 Ml.		
CSF No.	D *	P †	D/P
N2	10.0	0.8	12.5
N11	10.0	1.0	10.0
N13	9.5	0.7	13.5
N14	9.0	2.4	3.7
N16	5.0	0.6	8.3
N17	10.5	1.1	9.5
N18	13.0	1.0	13.0
N20	8.5	0.9	9.5
140	6.5	1.1	5.9
141	9.0	0.85	10.6
142	12.5	1.3	9.6
143	5.0	0.5	10.0
144	16.5	1.9	8.7
Mean			9.62
S. D.			2.94
S. E.			0.75

* Chemical data (method of Whitehead and Whittaker).
† Photometric data (our procedure).

In attempting to correct for the error, CSF glutamine concentrations based on standard photometric curves were obtained for a number of CSF's by linear extrapolation of such curves. For each such determination a quantitative chemical determination of glutamine was carried out on the same fluids. The method used in these determinations was provided to us through Drs. T. P. Whitehead and S. R. F. Whittaker, who made available to us their direct chemical method for glutamine determination before its publication date. No attempt was made to correct for hydrolysis of urea.

With both the colorimetric and the photometric data available, the information is subject to statistical evaluation, as shown in Table 2. The t value is 12.88, which with 12 degrees of freedom gives a p value of less than 0.001%. Thus, the mean ratio is significant for this set of data and may be legitimately used as a factor by which the values obtained by the photometric technique can be multiplied to give a corrected glutamine value.

RESULTS

The fluids which were studied can be divided roughly into three groups. One group consists of 26 fluids which can considered to be normal. These were obtained from subjects who had spinal punctures performed for spinal anesthesia, and were supplied by Dr. P. S. Marcus, of the Anesthesia Service, Boston City Hospital. The specimens were frozen immediately after collection. The patients ranged in age from 16 to 85, included both male and female subjects, and were screened so as to exclude the possibility of including any with neurological disorders or positive serological tests for syphilis. The results from the study of these normal fluids are summarized in Table 3. The qualitative and uncorrected quantitative data are presented. Not all the chromatograms yielded separations suitable for quantitation.

The second group consists of 12 spinal fluids from patients with a diagnosis of multiple sclerosis established by qualified experts. Most of these fluids were provided for us through Dr. B. W. Volk and Dr. F. M. Forster. The results of analysis of these fluids also appear in Table 3. When they are compared with the figures obtained with normal fluids, no significant quantitative difference and no consistent qualitative difference characterizes the multiple sclerosis group.

The third group of fluids studied is the largest. This group represents a random sampling of the fluids arriving at the CSF laboratory at Boston City Hospital, including some from multiple sclerosis cases. These fluids, labeled only with an identifying number, were supplied to us by Dr. J. M. Foley.

TABLE 3.—*Comparison of Amino Acids (Micrograms per Milliliter) for Normal and Multiple Sclerosis Groups*

	Normal Series (26 Fluids)					Multiple Sclerosis Series (12 Fluids)				
Amino Acid	Nf*	Nq†	Mean Value	Standard Deviation	Standard Error	Nf*	Nq†	Mean Value	Standard Deviation	Standard Error
Aspartic acid	26	5	0.4	0.1	0.014	12	5	0.4	0.17	0.074
Glutamic acid	26	9	0.6	0.3	0.10	11	6	0.6	0.24	0.099
Serine	26	18	1.6	0.70	0.16	12	12	1.6	0.69	0.20
Aminoacetic acid	26	17	1.0	0.45	0.11	11	10	1.1	0.49	0.16
Threonine	22	10	1.3	0.73	0.23	6	1	0.6	....	.....
Glutamine	26	18	7.1	5.0	1.27	12	12	10.0	4.4	1.25
Alanine	26	17	1.1	0.69	0.17	11	9	0.7	0.36	0.12
Tyrosine	22	7	0.8	0.32	0.12	11	8	2.0	1.42	0.82
Valine	26	16	0.7	0.52	0.13	12	7	0.5	0.26	0.10
Phenylalanine	23	9	2.1	4.1	1.40	8	5	1.1	0.39	0.17
Leucine	24	14	1.4	0.89	0.24	10	7	1.2	0.67	0.25
γ-aminobutyric acid	12	..	....	....	.....	6	..	....	....	.....
Histidine	14	..	....	....	.....	6	..	....	....	.....
Lysine	4	..	....	....	.....	2	..	....	....	.....
Asparagine	2	..	....	....	.....	1	..	....	....	.....
Cystine	5	..	....	....	.....	8	..	....	....	.....
Arginine	2	..	....	....	.....	2	..	....	....	.....
α-aminobutyric acid	8	..	....	....	.....	2	..	....	....	.....

* Number of fluids in which the amino acid was found.
† Number of fluids in which the amino acid was quantitated.

TABLE 4.—*Percentage Frequency of Appearance of Each Amino Acid in the Cerebrospinal Fluid of Each of the Five Groups* *

Amino Acid	Group 1	Group 2	Group 3	Group 4	Group 5
Aspartic acid	100	100	38	50	56
Glutamic acid	100	92	62	50	75
Serine	100	100	95	75	94
Aminoacetic acid	100	92	67	69	94
Threonine	85	50	76	56	31
Glutamine	100	100	100	100	100
Alanine	100	92	91	88	94
Tyrosine	85	92	81	69	81
Valine	100	100	95	88	94
Phenylalanine	89	64	67	62	75
Leucine	93	83	91	81	94
γ-aminobutyric acid	58	50	76	81	81
Histidine	54	50	71	81	50
Lysine	15	17	24	12	25
Asparagine	8	8	10	19	6
Cystine	19	66	29	37	19
Arginine	8	17	15	6	6
α-aminobutyric acid	31	17	33	44	50
Proline	0	0	0	6	0
Methionine sulfoxide	0	0	0	12	0

* Group 1: No disease of the nervous system.
Group 2: Multiple sclerosis.
Group 3: Neurological disease with normal CSF.
Group 4: Neurological disease with red cells in CSF.
Group 5: Neurological disease with CSF having abnormal gold curve or increased protein or both.

This random group represents fluids typically obtained from the spinal punctures performed in the course of everyday hospital procedure. Since most of these fluids were subjected to other types of examination, they can be separated into subgroups according to the laboratory findings.

The amino acid distribution in these subgroups is given in Table 4, Groups 3, 4, and 5, as compared with Groups 1 and 2, summarized from Table 3. The lower frequencies of certain amino acids in Groups 3, 4, and 5 (as compared with Group 1) may reflect inadequacies of analytical technique, since our first analyses were done on fluids from these groups. In general, no pattern of diagnostic significance emerges from these comparisons. The greater frequency of detection of cystine in the multiple sclerosis fluids is of borderline significance and is not explicable on the basis of present knowledge of the disease. This is not a consistent qualitative difference and could not be utilized as a diagnostic test.

If this sort of an investigation should ever be repeated or extended by ourselves or by others, the use of one-dimensional paper chromatography for quantitative study might be of advantage, although the identification of individual amino acids would be less certain. Kemali and Porcellati [35] report recoveries of alanine and leucine by one-dimensional procedures which compare well with our two-dimensional results when corrected for the losses indicated in Table 1.

SUMMARY

The procedure for the identification and quantitative estimation of the free amino acids of the cerebrospinal fluid, using ascending two-dimensional paper chromatography, is given in detail.

Average losses during the procedure have been determined and are shown in Table 1.

Spinal fluids from 26 surgical patients with no evidence of neurological disease have been analyzed by this procedure and compared with fluids from 12 well-authenticated cases of multiple sclerosis (Table 3).

No significant quantitative difference, or any consistent qualitative difference, characterizes the amino acid pattern of the multiple sclerosis group.

Proline and methionine were identified in a small percentage of the fluids studied which contained red cells, but in no other fluids (Table 4).

Dr. M. A. Derow made the statistical evaluations.

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News and Comment

ANNOUNCEMENT

Rorschach Test Workshops.—The Department of Psychology, University of Chicago, announces its 1955 summer workshops in the Rorschach Test, to be conducted by Dr. S. J. Beck the weeks of July 11-15 and July 18-22. The basic processes in test evaluation will occupy the first week's workshop, and it will demonstrate full test interpretations. The second week will be devoted to problems of advanced clinical interpretation, exemplified by children in more disturbed states and by adults in milder neurotic conditions. Workshop I may be taken by students at, or ready for, the intern level. Admission to Workshop II is limited to psychologists and psychiatrists in clinical positions or practice. Each seminar will meet for two two-hour sessions per day. For full information, write to the Executive Secretary, Department of Psychology, The University of Chicago, 5728 S. Ellis Ave., Chicago 37.

GENERAL NEWS

Congress of Neurological Surgeons, Inc.—At the Fourth Annual Meeting of the Con-Neurological Surgeons, Inc., held at the Waldorf-Astoria Hotel, in New York, Nov. 4, 5, and 6, 1954, the following officers were elected: president, Dr. Donald B. Sweeney, Birmingham, Ala.; vice-president, Dr. Bland W. Cannon, Memphis; secretary-treasurer, Dr. Philip D. Gordy, Wilmington, Del.; executive committee, Drs. M. P. Sayers and Robert Mabon of Columbus, Ohio, and Atlanta, respectively.

STUDIES ON HEADACHE

Variations in Fluid and Electrolyte Excretion in Association with Vascular Headache of Migraine Type

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and
H. G. WOLFF, M.D., New York

IT HAS long been recognized that many patients with the migraine type of vascular headache undergo changes in fluid balance and fluid distribution during the headache attack. Local changes in fluid distribution are evidenced by (1) puffiness of the face, (2) periorbital edema, and (3) localized patches of edema about the temporal and frontal regions. More widespread fluctuations in fluid balance are evidenced by (1) swelling of the fingers, so that rings are hard to remove and shoes are tight; (2) weight gain prior to headache; (3) occurrence in some women of headaches in association with the menses, often coupled with a state of hydration, and (4) diuresis at the "peak" of the attack and as the headache subsides.[1]

The headache itself results from local vascular phenomena involving dilatation of the cranial arteries. That various types of vessels are involved, if not painfully, may be surmised from the blanching or flushing of the face, coldness of the hands, and sensations of "chilliness" which may accompany headache.[1]

Pfeiffer and his co-workers[2] studied changes in blood volume during headache by determining serum proteins and hematocrit readings during headache and after treatment. Since both values decreased with treatment, they concluded that blood volume had been decreased during the phase of headache. They also determined the serum potassium concentration and found it slightly less during headache than after treatment. Campbell, Hay, and Tonks[3] reported a rise in serum sodium before and during headache to levels of 373 mg. per 100 cc. In contrast to the report of Pfeiffer, they found a decrease in serum proteins during the headache phase and attributed this to overhydration. Lusk, Viar, and Harrison[4] reported an instance of migraine occurring incidentally during the course of tests of renal function in which 200 cc. of 0.14 N saline was ingested hourly while leg compression was being applied. They reported a striking decline in sodium excretion and a decrease in urine volume in association with this headache.

Studies were therefore undertaken to define the nature and magnitude of the fluid and electrolyte variations associated with vascular headache.

METHOD

In order to study all phases of the attack of migraine headache, we observed subjects over periods of 7 to 18 days. They continued to perform their daily work, collecting all urine voided and pooling this into four specimens daily. The collection periods ended (1) upon arising in the morning, (2) before the noon meal, (3) before the evening meal, and (4) before retiring for the night. Records were kept of food and fluid ingested, of events and muscular activities of the day, of behavior and emotional responses to these events and activities, and of the onset, duration, fluctuations in intensity, and termination of headache. Sodium and potassium determinations were performed in duplicate on all urine specimens, using a Barclay flame photometer.[5] Creatinine determinations were made in duplicate, using a modification of the technique of Bonsnes and Taussky.[6] Ten subjects, experiencing 28 headaches, were studied. The results in 8 subjects, with 26 headaches, are included here. Data on the remaining two subjects, with two headaches, were technically unsatisfactory.

This study was made possible in part by grants from the Commonwealth Fund.

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RESULTS

OBSERVATION 1.—Mrs. E. P., a 25-year-old housewife with two children, was studied for two weeks, between March 27 and April 8, 1953. She had suffered no serious illness, her only complaint being recurrent vascular headaches of the migraine type, which had first occurred during adolescence and which were becoming increasingly frequent and severe. During the period of observation she had three attacks. On the morning of March 29 she overslept and had to rush to get to church on time. During the service she developed a mild headache, of which she said: "Really, it was nothing at all." This headache subsided promptly. It was not preceded by weight gain and was associated with no significant variation from the average in excretion rates of water, sodium, potassium, and creatinine. However, all phases of this headache—before, during, and after—were included in the one morning urine collection.

The following days she had many duties to perform and felt "tense" most of the day. She retired feeling "worn out" from the exertions of the day and awoke the following morning with a headache of moderate intensity. This headache subsided during the afternoon, while she was engaged in housework. No weight gain preceded it, and no weight loss followed it. Figure 1 shows the fluctuations in urine volume and in renal excretion of sodium, potassium, and creatinine which accompanied it. Excretion rates for all substances studied were low prior to the onset of headache and high during the period of subsidence.

During the succeeding days life was "hectic" for her. She disliked interruptions in her routine. The landlord came to redecorate the apartment, and this made her routine of work impossible. She could not "stand criticism" from friends or relatives about her housekeeping. Yet it was impossible to keep her house in order during the repairs which were being made, and she was "constantly in fear" of some unexpected visitor arriving to find her home "a shambles." Also, the children "chose" this period to "catch cold" and become unusually demanding upon her time, patience, and energy. During this period she gained 2 lb. (0.9 kg.) in weight, due almost entirely to an increase in her fluid intake. Despite careful recording of all fluids imbibed, she was not aware of this increased intake until it was pointed out to her later. Though her daily fluid intake increased from 2400 to 3400 cc., there was a slight decrease in the 24-hour output (Table 1). She retired late on April 4, having prepared Easter eggs for the children, despite feeling exhausted after the several days of domestic confusion. On retiring she felt "worn out" but satisfied, knowing that the apartment repairs and redecorations were complete, the house in order again, and all the Easter preparations accomplished. Easter Sunday, while at Communion, she developed a severe, throbbing headache, which continued throughout that and the succeeding day. By Tuesday she was feeling slightly better, but while traveling home after visiting her physician she had an acute exacerbation of head-

TABLE 1.—*Twenty-Four-Hour Fluid Intake and Output in Subject E. P.*

Date	Morning Weight, Lb.	Fluid Intake, Cc.	Urine Output, Cc.	Comments
3/27	133	2190	1990	Birthday party for child; patient then relaxed
3/28	132	2010	1620	Landlord began work in apartment
3/29	132	1620	1440	Overslept; rushed to church—marginal headache
3/30	132	2400	1040	"Tense day"
3/31	132	2460	1740	Moderate headache in morning, gone in afternoon
4/1	132	2520	1580	Quiet day
4/2	132	3400	1164	Many difficulties: refrigerator broke down, sewing machine wouldn't work; had to go to hospital
4/3	133	3120	1695	Landlord painting; house "a shambles"
4/4	134	2280	1975	Continued painting and plastering
4/5	134	1710	1680	Severe headache began during Communion
4/6	134	1410	1155	Headache continued, began improving during the night
4/7	132	1200	1775	Awoke improved; brief, "blinding" headache in morning, with subsidence during afternoon
4/8	132	....	1260	No headache

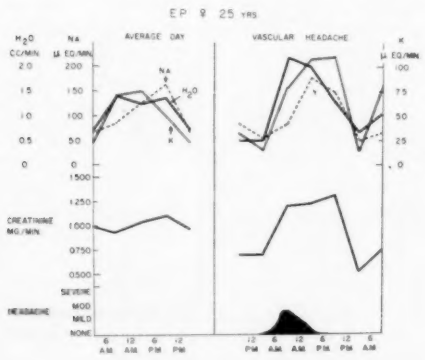

Figure 1

ache. She had to mobilize herself to keep at work all day, describing this as a "harrowing experience" despite gradual subsidence of the headache during the afternoon. One child was ill, and the other refused to eat anything. Though she had two days of housework to finish in one, her headache had diminished by evening, and she felt fatigued but comfortable. A striking decrease in creatinine excretion occurred during the brief period of "blinding" headache.*

A comparison of excretion rates of the substances studied during the phase of onset of headache or just preceding and during the phase of subsiding headache is given in Table 2.

Comment.—A mild, transitory headache and a moderately severe headache of short duration were observed in this patient following short periods of increased work and of headache. Excretion rates of water, sodium, potassium, and creatinine were low prior to headache and high during the phase of subsidence of headache (Table 2).

OBSERVATION 2.—M.S., a 28-year-old housewife and physician, was studied for 46 days, during which she had one mild headache. This headache followed a prolonged period of exhausting activities, associated with feelings of "tension" and "depression." Two days after termination of these activities, she awoke feeling "better than usual" but developed a mild headache on arising. This persisted throughout the morning hours. Excretion rates of water, sodium, and potassium during these morning hours were lower than they had been during the preceding night. She felt generally "tired" and "lacking in energy" through the morning, but had to force herself into action during the afternoon in caring

TABLE 2.—*Fluid and Electrolyte Excretion in Subject E. P.*

Phase	H_2O, Cc./Min.	Na, μEq./Min.	K, μEq./Min.		Creatinine, Mg./Min.
			Day	Night	
Average nonheadache day	1.14	109	68	21	1.029
Before headache	0.69	70	..	17	0.891
With headache subsiding	1.62	162	93	..	1.164

TABLE 3.—*Fluid and Electrolyte Excretion in Subject M. S.*

Phase	H_2O, Cc./Min.	S. D.	Na, μEq./Min.	S. D.	K, μEq./Min.		S. D.	Creatinine, Mg./Min.
					Day	Night		
Average of 47 asymptomatic days	0.76	±0.17	96	±20	54		±5	.....
Two days before headache	0.45	.....	31	....	23	18	...	0.920
Two days with subsiding headache	1.48	.....	130	....	72	..	...	1.014

responsibilities associated with feelings of "tension." These two headaches were not accompanied by fluctuations in weight. The first was too brief for study by the method used in this report. The second was preceded by low excretion rates of water, sodium, potassium, and creatinine and was followed by high excretion rates of these substances. A third headache, of high intensity lasting three days, occurred after three days of domestic disarray, disorganization, and disrupted routine. Weight gain occurred during the few days immediately preceding headache, and weight loss accompanied subsidence for her children and entertaining unexpected, but welcome, guests. Excretion rates of water, sodium, and potassium were considerably increased during this period (Fig. 2), and her headache temporarily abated. With an evening "let-down," the headache

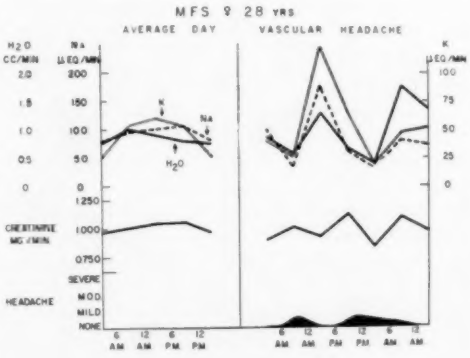

Figure 2

* Creatinine excretion averaged 0.75 mg/min. during this period, as compared with 1.09 mg/min. in the period before and 1.03 mg/min. in the subsequent period. This decrease occurred despite an increase in urine volume.

recurred and did not subside completely until the following morning, during a period of relaxation.

A comparison of excretion rates of water, sodium, potassium, and creatinine during the period prior to onset of headache and during its early phases with the period of subsidence of headache is given in Table 3. Excretion rates of all these substances were low prior to headache and high during the phase of final subsidence.

Comment.—A mild headache occurred in this subject after prolonged feelings of "tension" and "depression." A transient subsidence of headache occurred with mobilization for work. This was accompanied by a slight decrease in creatinine excretion and by a considerable increase in potassium excretion. With "let-down," headache recurred, to disappear the following day, during a period of relaxation associated with water diuresis.

OBSERVATION 3.—B. H., a 29-year-old healthy male physician, was studied for a period of 14 days. During this period of observation one episode of "heavy-headedness" was recorded. This period was characterized by a feeling of fullness in the head and by general lassitude and fatigue, such as frequently accompanied a vascular headache in this subject. However, the subject felt no actual pain. On January 16, with his family ill and household responsibilities falling on his shoulders, he felt "tense" and depressed and gained 2 lb. in weight. The following day was spent performing unfamiliar and distasteful routines: cleaning house, caring for the children, answering the telephone and doorbell, and preparing meals. He retired, feeling "tense," depressed, and lacking in energy. He awoke the following morning heavy-headed. This day went more smoothly and quietly. During the afternoon he relaxed, listening to music. The heavy-headed feeling never developed into a headache but subsided altogether during the course of the afternoon. Creatinine excretion remained low throughout the period of heavy-headedness, returning toward the average as this feeling subsided. Excretion rates for water, sodium, and potassium were moderately decreased prior to the sensation of heavy-headedness and during it, with a sharp increase in excretion during the period of subsidence (Table 4).

Comment.—A period of "heavy-headedness" without headache was associated in this patient with fluctuations in rates of excretion of water, sodium, potassium, and creatinine similar to those recorded in other subjects in association with headache.

OBSERVATION 4.—Mrs. E. L., a 52-year-old telephone supervisor, who had suffered severe headache attacks since the age of 12, was studied for seven days while hospitalized because of her migraine. She was having recurrent attacks of severe headache with but brief intervals between them. The series of headaches reported here developed in a setting of home difficulties. In addition to her work during the day, the patient was caring for her mother-in-law nights and weekends. The mother-in-law was bedridden and irascible; her own children refused to help any further in her care because she was so demanding and so lacking in gratitude. During the period of observation there were six recurrences of her headache. Excretion rates during the various phases of these six headaches are given in Table 5.

TABLE 4.—*Fluid and Electrolyte Excretion in Subject B. H.*

Phase	H_2O, Cc./Min.	Na, μEq./Min	K, μEq./Min.	Creatinine, Mg./Min.
Before "heavy-headedness"	0.59	78	35	0.891
During "heavy-headedness"	0.52	74	58	0.861
With subsidence	0.88	203	85	1.052

TABLE 5.—*Fluid and Electrolyte Excretion in Subject E. L.*

Phase	H_2O, Cc./Min.	Na, μEq./Min.	K, μEq./Min.	Creatinine, Mg./Min.
Without headache	0.72	38	35	0.956
Before or early in headache	0.46	19	18	0.696
Subsiding headache	1.19	40	49	0.878

Comment.—Recurrent headaches in this patient were preceded by low excretion rates of water, sodium, potassium, and creatinine. Subsiding headache was accompanied by high rates of excretion of water and potassium with creatinine excretion increasing toward the nonheadache level.

OBSERVATION 5.—N. S., a 19-year-old secretary, was studied for 18 days while having recurrent

headaches. Remissions lasted only a few hours. Eleven recurrences were studied during the period of observation. Excretion rates were uniformly low before each recurrence and uniformly high during each period of subsidence. During the headache, excretion rates of water, sodium, and potassium remained in the midrange or low, while creatinine excretion fluctuated widely. Table 6 presents a summary of the data on this subject.

Comment.—In this subject, suffering from recurrent headache, each recurrence was accompanied by decreased rates of excretion of water, sodium, potassium, and creatinine; and each subsidence of headache, by increased rates of excretion of water, sodium, and potassium, with creatinine excretion returning to average levels.

In three other subjects, mild and transitory headaches were observed to be associated with similar fluctuations. When data for the 26 headaches included in this report were combined, the average rate of urine flow preceding and during the early phases of headache was 0.47 cc/min., as compared with an average urine flow of 1.44 cc/min. during the subsidence of headache. The average rate of sodium excretion before headache was 47 μEq/min., as compared with 133 μEq/min. during subsidence. The average rate of potassium excretion before headache was 26 μEq/min. as compared with 68 μEq/min. during subsidence. Major fluctuations in creatinine excretion also occurred, with an average rate of excretion of 0.738 mg/min. before headache and 1.044 mg/min. during subsidence of headache. The rate of creatinine excretion prior to headache is of low value, but the rate during subsidence is similar to the average rate observed during nonheadache periods.

TABLE 6.—*Fluid and Electrolyte Excretion in Subject N. S.*

Phase	No. of Observations	H_2O, Cc./Min.	Na, μEq./Min.	K, μEq./Min.	Creatinine, Mg./Min.
Before headache or early in its course	11	0.38	51	30	0.642
During headache	24	0.62	81	34	1.025
Subsiding headache	10	1.46	163	61	0.995

GENERAL COMMENT

In these observations, headache occurred in settings of increased work and responsibility, in association with unpleasant tasks which the subject felt he had to perform, or after outbursts of anger, when the subject was feeling depressed and dejected. These situations were associated with feelings of "tension" and "depression." These feelings might be of short duration (a few hours in the case of E. P. prior to the first headache) or of long duration (several weeks in the case of M. S.). The headache usually began after the noxious stimulation had been eliminated. At such times the subjects usually complained of fatigue and lack of energy and did not feel free of "tension" despite changes in the setting. In one of the instances reported, the subject reported feeling much better than usual just prior to onset of headache.

Weight gain prior to headache was unpredictable. No gain was recorded in two of the subjects: for the first two headaches occurring in E. P. and the mild headache recorded by M. S. Weight gain, when it did occur, was variable in the time prior to headache at which it occurred. In B. H. and before the last headache in E. P., a 2 lb. weight gain occurred two days before headache. In one subject it occurred at least a week before headache, with weight then remaining constant at the higher level until the headache had subsided. The time of weight gain is unknown in Subjects E. L. and N. S.

Weight loss was also unpredictable. None was recorded in association with the headaches not preceded by weight gain. Weight loss did occur with subsidence of headache on several occasions in N. S. With B. H., weight loss did not occur until two days after subsidence of headache. However, a diuresis did accompany subsidence of headache in this subject, even though not sufficient to produce weight loss at that time. Weight loss was recorded the day before

complete subsidence of headache in E. P. (third headache). This was a gradual loss without any dramatic diuresis, and the headache diminished in intensity during the diuresis. The following morning a "blinding" headache (high intensity) of brief duration occurred. Subsidence of this attack was accompanied by major diuresis and no further recurrence of headache.

Retention of fluid and electrolyte, in varying amounts, preceded all headaches in this series. This was not related to intensity of pain, for, indeed, headache had not yet begun. It was similar in every way to the retention noted in the same subject, and in others not subject to migraine headaches under conditions of increased work demands, associated with a restless, sometimes overactive, behavior pattern and with feelings of "tension" and "depression."

Diuresis of fluid and electrolyte in varying amounts and proportions accompanied subsidence of the majority of headaches. Variations in the excretion rate of potassium were sometimes very striking. On four occasions the major variation in excretion during the period of subsiding headache was an increase in potassium excretion. Subsidence of headache in the majority of instances was accompanied by a diuresis of fluid and electrolyte in varying amounts and proportions. Occasionally major diuresis was delayed for 24, or even 48, hours after elimination of headache, though a diuresis of minor proportions accompanied the actual subsiding phase.

Alterations in creatinine excretion were also noted in association with vascular headache. Rates of creatinine excretion before headache and during the early phases of headache were much reduced, sometimes to 25% or 30% of average "nonheadache" values. Subsidence of headache was accompanied by return of these values to average levels. Rates of excretion higher than those observed during nonheadache periods were not noted.

Although the results described above are usual during vascular headache attacks, it is unlikely that the fluid and electrolyte changes are significant in the genesis of the attack, or that they are involved in the mechanisms of the nausea and vomiting, visual disturbances, or the pain experienced. Indeed, during at least one carefully studied attack, a sizable diuresis of water, sodium, and potassium preceded the onset of headache. In other studies,† also, it was shown that diuresis induced by a chemical agent during the period of weight gain, and several days before the beginning of the attack, neither altered the usual time of occurrence nor the intensity and duration of the attack. Furthermore, diuresis induced immediately before or during the preheadache phase in no way modified the quality, intensity, or duration of the subsequent headache. On the other hand, fluid retention, edema, and weight gain following administration of vasopressin (Pitressin) in two persons subject to headache attacks, during a period when they were having frequent headaches, did not precipitate attacks. Therefore, it seems most likely that the changes in fluid and electrolyte output and in renal circulation suggested by the creatinine studies are accompaniments of widespread bodily adaptations occurring during or after stressful periods, of which preheadache and headache phenomenology in certain susceptible persons is but a single aspect. In short, the fluid, electrolyte, and renal changes are concomitant, rather than causative, factors of the migraine attack.

Other studies from this clinic demonstrate that the fluid, electrolyte, and renal circulation changes above described are most likely linked with altered adaptive patterns. These include a variety of behavior patterns, attitudes, and feelings in reaction to stressful life circumstances, sometimes linked with headache and other disorders, but not specifically or causally related.

The local changes in the subcutaneous tissues of the forehead and face exhibited as puffiness, pitting edema, and tenderness of the tissues during attacks are not part of the general alteration of fluid and electrolyte metabolism. These cranial effects are intimately linked with the local mechanism of pain

† Ostfeld, A., and Wolff, H. G.: Work in preparation.

and occur regardless of general fluid accumulation or diuresis. Local vascular changes result in the accumulation of fluid and of a pain-threshold-lowering substance in the tissue, which, in combination with local arterial dilation, causes the characteristic headache of the attack.

SUMMARY AND CONCLUSION

Eight persons subject to vascular headache of the migraine type had technically satisfactory studies made before, during, and after 26 headache attacks, with the following results:

1. Decreased rates of excretion of water, sodium, potassium, and creatinine were usually observed prior to and during the early phases of vascular headache of the migraine type.

2. Increased rates of excretion of water, sodium, and potassium were usual with subsidence of the headache attacks.

3. Creatinine excretion returned to "normal" values during subsidence of headache, with four exceptions. On these four occasions potassium excretion was high.

4. Weight gain prior to the headache attack was common but not invariable. It sometimes occurred well in advance (7 to 10 days) of the onset of headache.

5. Weight loss with subsidence of headache was usual. However, it was sometimes delayed 24 to 48 hours.

It is concluded that the described fluid, electrolyte, and renal changes are not causally or mechanistically related to the onset, intensity, or duration of the migraine attack. Instead, they are manifestations of the widespread bodily changes accompanying adaptive reactions during and after stressful periods. The migraine attack is a concurrent, but independent, feature.

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CHOROID PLEXUS AND ARTERIAL PULSATION OF CEREBROSPINAL FLUID

Demonstration of the Choroid Plexuses as a Cerebrospinal Fluid Pump

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IT IS COMMON knowledge that the cerebrospinal fluid pulsates with each heart beat, bu. this phenomenon has received little detailed attention. This paper presents a study of the cerebrospinal fluid pulsation secondary to the arterial pulse. The site of transfer, magnitude, and possible clinical importance of this pressure pulse are demonstrated and considered.

This problem was first extensively investigated by Antoni * in Sweden, who examined the cerebrospinal fluid pulse in many conditions, particularly spinal block. O'Connell,[9] in England, also seriously considered this problem. He pointed out that most methods for measuring the pulsations are inadequate because of the damping effect of the manometers generally in use. Turchetti,[14] in Italy, used a method of photographing the meniscus of an open-bore manometer to measure the pulsations. However, this did not avoid the displacement of CSF into an open-bore tube, which is one of the primary sources of the damping effect.

Gerlach,[6] in Germany, used sensitive microphones to pick up the pulsations of the CSF in the lumbar region and in the cranium (measured through trephine holes). He studied the configuration of the pulse wave in some detail and showed how it changed with variations in the intracranial pressure. He did not, however, consider the magnitude of the pulsation. Goldenshon [7] and Ryder [11] and their associates observed the changes in the magnitude of the CSF pulsation associated with changes in intracranial pressure.

The damping effects of the open manometers have been eliminated in this study by using isovolumetric electronic manometers. This method has made it possible to study the magnitude and configuration of the CSF pulsation in some detail with great accuracy.

MATERIALS AND METHODS

Intraventricular, cisternal, and lumbar subarachnoid CSF pressure measurements were made on a group of dogs (normal and hydrocephalic) before and after choroid plexectomy, and on a series of patients undergoing neurological investigation and neurosurgical procedures. Pressures were measured with Sanborn electromanometers and recorded on a Sanborn Polyviso recorder. Electrocardiograms were recorded simultaneously for purposes of timing the pulsations in relation to other physiological events.

All of the animal surgical procedures were carried out with the animals under intravenous pentobarbital (Nembutal) anesthesia. The choroid plexectomy and ventriculotomy were made through a parietal craniectomy measuring 3 by 2 cm. Bilateral choroid plexectomy was done as a single operation through incisions in the occipitoparietal cortex. Absorbable gelatin sponge U. S. P. (Gelfoam) soaked in kaolin was used to plug the foramen of Monro. The effectiveness of the plugs was tested by injecting dye into one ventricle and observing the fluid from the other ventricle to see whether the dye passed into it. Postmortem examination was carried out on all the dog brains to determine the completeness of the choroid plexectomies.

The cisternal CSF pressure was always measured with a 19-gauge needle introduced into the cisterna magna with the dog on his right side on a flat table. A rubber tube with a small glass U attached to one end was filled with 0.8% NaCl solution and attached to the needle without loss of CSF.

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* References 1 and 2.

The pressure was then read with the table top as zero. The midsternal height (taken as the measure of the height of the right atrium above the table) was subtracted from this value. The recorded pressure was then that pressure above the midsternal or right atrial level.

RESULTS

Transfer of Arterial Pulse Wave to Cerebrospinal Fluid.—The intraventricular pulse appears just after the pulse wave in the carotid artery, and it has a similar shape (Fig. 1).

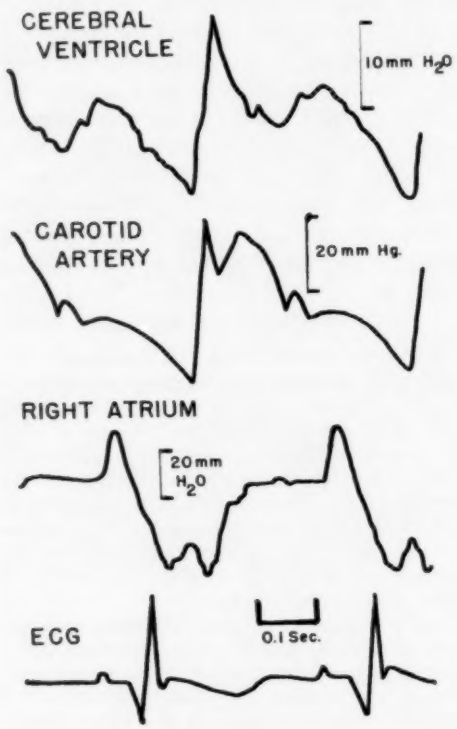

Fig. 1.—Simultaneous EEG and pulse recordings made from the lateral cerebral ventricle, the carotid artery, and the right atrium.

This configuration and timing demonstrate that the CSF pulse is produced by the arterial pulse. In a normal patient recordings taken simultaneously from the cerebral ventricles, the cisterna magna, and the lumbar subarachnoid space show this arterially induced pulse in all regions (the configuration magnitude will be considered later). However, in patients with noncommunicating hydrocephalus or absence of ventricular pulsations the pulse is absent in the lumbar region. This is in agreement with the earlier observations by Antoni,† who described the absence of the arterial pulsation in the spinal subarachnoid space below a block.

The choroid plexus was demonstrated to be the site of transfer of the arterial pulse to the CSF by measuring the ventricular CSF pulse in three hydrocephalic dogs before and after the choroid plexuses of the lateral ventricles were excised. A control experiment was done in two dogs in which the ventricles were opened but the choroid plexus was left intact. These experiments showed that if the choroid plexus was not damaged, the pulse wave did not change after operation, but if the choroid plexus was removed, the characteristic pulse wave disappeared. The possibility that this change in CSF pulse was caused by changes in intracranial circulation or in intracranial pressure was eliminated by the following experiment: A unilateral choroid plexectomy with plugging of the foramen of Monro was carried out in six dogs, and after recovery from the surgery the CSF pulse pressures were recorded simultaneously from the two ventricles. Unilateral choroid plexectomy with an open foramen of Monro and unilateral ventriculotomy without plexectomy were done as control experiments. These experiments showed that when the choroid plexus had been removed from a lateral cerebral ventricle and the foramen of Monro plugged, no pulsation, or only a very small pulsation, could be recorded from that ventricle, while, at the same time, a normal pulsation could be recorded from the opposite ventricle (Fig. 2).

If the foramen of Monro had been left open, the CSF pulse was recorded from both the ventricles, but it was slightly lower in the ventricle without a choroid plexus. Unilateral ventriculotomy without plexectomy had no effect on the CSF pulse.

† References 1 and 2.

The possible contribution of the basal arteries to the CSF pulsation could not be determined from these data, for in the patients with aqueduct block the status of the subarachoid pathways at the base of the brain was uncertain, and in the dogs the procedures used to produce hydrocephalus cause occlusion of these pathways, and probably partial destruction of the choroid plexus of the fourth ventricle. This point was in part clarified by recording the cisternal pulse pressure on a series of normal dogs before and after choroid plexectomy of the lateral ventricles or control ventriculotomy. The control animals showed no change in the CSF pulse after operation, but in the plexectomized animals the cisternal pulse was reduced over 60%. The choroid plexuses of the third and fourth ventricles, which constitute about 30% of the total dog choroid plexuses, remained, and therefore any contribution to the CSF pulse by the basal arteries is probably relatively small.

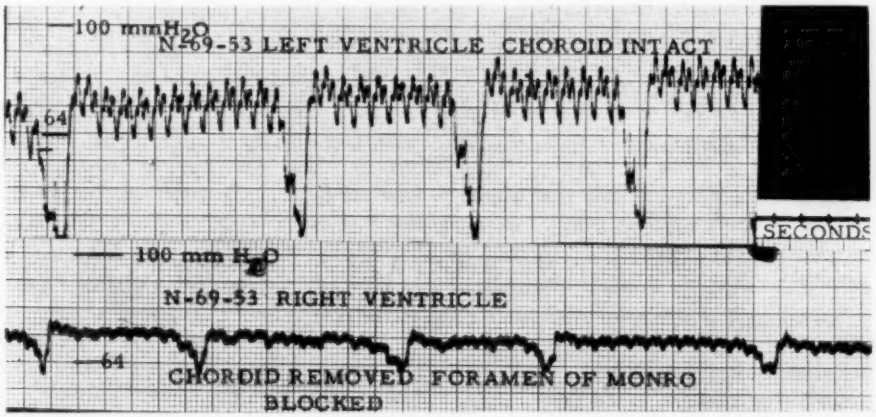

Fig. 2.—Recordings of the intraventricular pulse from the dog with the choroid plexus of the right lateral cerebral ventricle removed and the right foramen of Monro plugged. The recordings were made consecutively, so that the respiratory pressure changes are not synchronous.

Configuration and Amplitude of the Arterially Induced Cerebrospinal Fluid Pulse.—While the ventricular pulse does to some extent approximate the carotid pulse, it is also seen that in its late phase there is a peak which coincides with the atrial contraction (Fig. 1). This is presumably the effect of increased venous pressure; however, this phenomenon is absent in many records. The reasons for this variation are not clear, and await further study. There are usually two small peaks in the decending phase, as described by Gerlach,[6] and in some records there are numerous other small pulsations superimposed in the arterial pulse, particularly in the descending phase. These are of uncertain origin, possibly resulting from movements of the patient, changes in venous pressure, or echoes of the pulse wave in the skull.

The cisternal pulse wave has less amplitude than, but the same configuration as, the ventricular CSF pulse. The lumbar CSF pulse wave has a considerably different form, with the peak much lower and later than in the ventricular pulse (Fig. 3). This shows that during the pulsation a pressure gradient is established throughout the CSF system, with the highest pressure within the cerebral ventricles. The absolute magnitude of this gradient is related to the size of the ventricular pulse, but the relative magnitude is fairly constant. In a group of 20 patients (age 1 month to 60 years) on whom simultaneous ventricular and lumbar CSF pulse measurements were made, the amplitude of the lumbar pulsations averaged about 40% of the ventricular pulse.

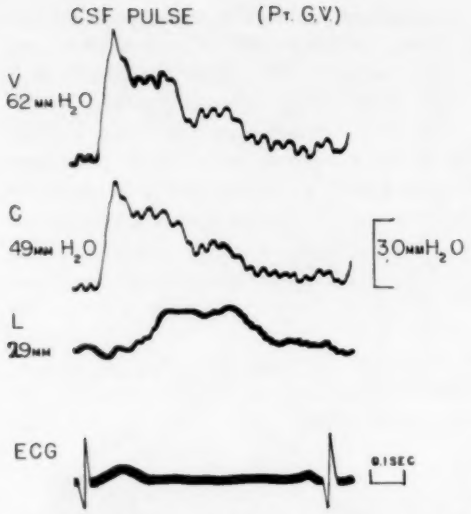

Fig. 3.—Simultaneous ECG and pulse records from the cerebral ventricle, cisterna magna, and lumbar subarachnoid space of an 11-year-old boy. The pulses, in millimeters of water, are ventricular, 62; cisternal, 49, and lumbar, 29.

This pulsating gradient imparts a to-and-fro motion to the CSF and acts as an unvalved pulse pump forcing the fluid out of the ventricles. The net flow resulting from such a pumping action would depend upon the amount of CSF removed from the subarachnoid pathways during each pulse. The concept of the arterial pulse acting as a pump was suggested by O'Connell.[9] However, he thought that the brain was squeezed from without by the pulsation of the large arteries at the base of the brain. These experiments show that the reverse is true; the fluid is forced from within outward.

The experiments presented here, the work of Antoni ‡ and Goldenshon and associates,[7] show that the CSF pulse seen in the lumbar region is generated intracranially by the arterial pulsation of the blood, and not through local venous pressure changes, as suggested by Turchetti.[14] The difference in shape and magnitude between the ventricular CSF pulse and the lumbar CSF pulse is the result of attenuation by distance and damping by the slightly elastic and loosely supported dural sac, or by small changes in the craniospinal blood volume, or perhaps by the escape of small amounts of CSF from the subarachnoid space.

The amplitude of the intraventricular CSF pulse is affected by several things. There is a direct relationship to growth, as might be expected. This can be shown by using body length as an index of growth and plotting it against the amplitude of the intraventricular pulse (Fig. 4).

The amplitude of the intraventricular CSF pulse wave are affected by changes in the intracranial pressure. As the pressure increases, the amplitude of the pulse increases and the secondary peaks become more prominent. This has been confirmed by the previous observations of Gerlach,[6] Goldenshon and co-workers,[7] and Ryder and associates.[11] The explanation of this lies in the physical nature of the CSF system. The volume of the CSF is not fixed, and it can be altered by changes in the craniospinal blood volume, by changes in the volume of the brain and spinal cord, by stretching of the spinal meninges, and by bulging of the fontanel in infants. Under normal conditions the system is not fully distended, and minor fluctuations of CSF volume can be easily absorbed by an equal change of one or a combination of the volume-controlling variables. These mechanisms serve to damp the normally occurring CSF pulse; but as the intracranial pressure increases, the CSF

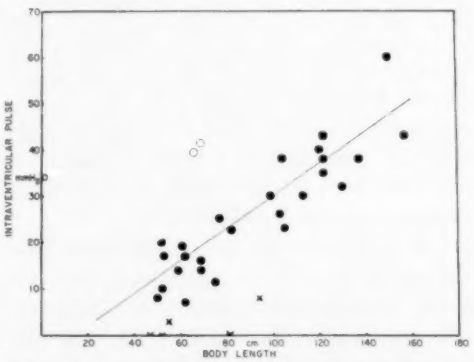

Fig. 4.—Plot of intraventricular pulse pressure *vs.* body length. This shows the direct relationship between growth and the intraventricular pulse pressure. The open circles and crosses are over two standard deviations from the least square trend.

‡ References 1 and 2.

space becomes more and more fully distended and the pulse cannot be damped, so that it appears larger and with more detail of the originating wave (the carotid arterial pulse). The effect of damping can be illustrated if the pulse pressure is measured in one ventricle and an open-bore manometer attached to a needle in the opposite ventricle. The pulse is then recorded with the manometer open and closed. This type of measurement is illustrated in Figure 5.

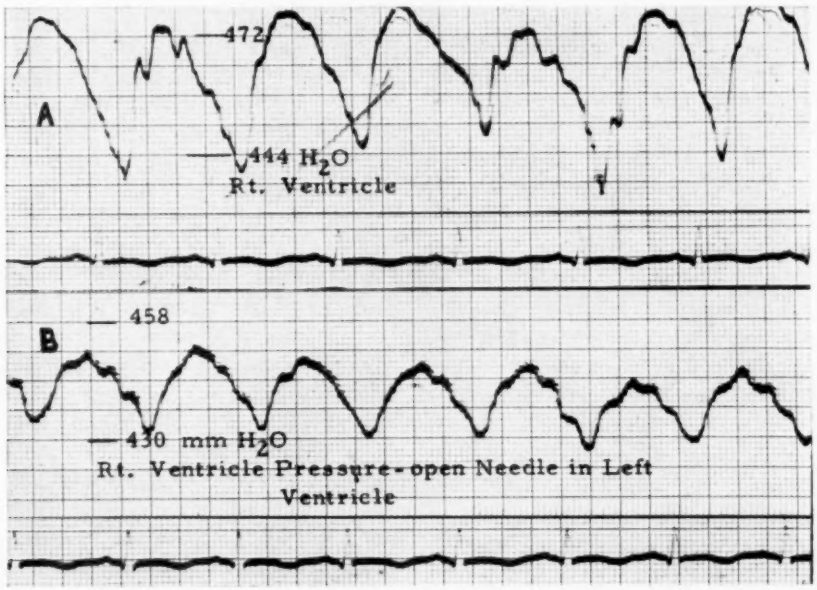

Fig. 5.—Intraventricular CSF pulse in a hydrocephalic child with increased intracranial pressure. There were needles in both ventricles. The right ventricle was connected to the electronic manometer and the left ventricle connected to a full open-bore Ayer manometer. *A* is a record of the intraventricular CSF pulse with valve to the Ayer manometer closed; *B* is the pulse after the Ayer manometer was opened. No fluid had been removed. With the needle open the pulse has been reduced from 50 to 28 mm. H_2O.

This patient had a pulse pressure of 50 mm. H_2O with the manometer closed, but with the manometer open the damping effect of the manometer was sufficient to cause the pulse pressure to drop to 28 mm. H_2O.

The damping effect of the open fontanel is well demonstrated by the change in shape of the wave after the closure of the fontanel. In infants the pulse wave is rounded and without the additional peaks in the descending phase. When the fontanel closes and the skull becomes a relatively more solid box, the pulse wave becomes more sharply peaked and the peaks of the descending phase become prominent.

Changes in the arterial pulse pressure and the state of the vessels will change the CSF pulse. Goldenshon and associates[7] have reported that the cisternal CSF pulse pressure of dogs was markedly increased by the inhalation of CO_2. Several things contribute to this change. There is a change in the state of the vessels caused by the CO_2; the general intracranial blood flow increases, and the mean CSF pressure rises. Which of these factors is the most important is not known at present.

Contribution of the Cerebrospinal Fluid Pulse to the Mean Intracranial Pressure.—The pulsations of the choroid plexuses seem to make a small but real contribution to the intracranial pressure. This was determined by measuring the cisternal CSF pressure before and after removal of the choroid plexuses of the lateral ventricles of 22 dogs.

A control operation, ventriculotomy without plexectomy, was done on five dogs. The mean intracranial pressure in a series of 55 dogs was found to be 99 mm. H_2O. The range was from 45 to 145 mm. H_2O, with a standard deviation of 18 mm. H_2O. After choroid plexectomy the mean pressure of the group was 72 mm. H_2O. This reduction in pressure is statistically significant and is probably a true effect. The reduction of pressure was not an acute reaction to the surgery, but was maintained as long as the measurements were made. The mean intracranial pressure of the dogs after the control ventriculotomy was 95 mm. H_2O, their preoperative level. These data are summarized in Table.

Effect of Bilateral Choroid Plexectomy on the Mean Cisternal Cerebrospinal Fluid Pressure of Dogs

	No.	Range of Pressure, Mm. H_2O	Mean Pressure, Mm. H_2O	Standard Deviation	*P*
Normal dogs	55	45-145	99	18	.....
Normal dogs after bilateral ventriculotomy	5	80-110	95	..	.....
Normal dogs after bilateral choroid plexectomy	22	50-100	72	19	0.001
Hydrocephalic dogs	15	.....	149	..	.....
Hydrocephalic dogs after bilateral choroid plexectomy	7	.....	75	..	.....

COMMENT

The pulsation of the CSF is generated by the filling and draining of the choroid plexuses. Any changes in the blood flow, the blood pressure, the size of the choroid plexus, or the state of the vessel walls will affect this draining and filling and be reflected in the CSF pulse. The pulse is also affected by the general intracranial pressure, and anything which changes it will, in turn, cause changes in the CSF pulse, whether the pressure is increased from a mass or from a blockage of CSF flow. These various effects were demonstrated with a mechanical model.[3] This model also showed that the pulse effects were independent of flow of CSF through the system as long as the outlet was of sufficient size. If the outlet was too small, the pressure rose from the accumulation of fluid, and this, in turn, had its effect on the pulse height.

Any net flow of CSF resulting from the pumping action of the choroid plexuses is, of course, very small in amount and depends upon the amount of CSF removed from the subarachnoid pathways. This pumping action is not vital to the CSF circulation, as there are many adults who have had a choroid plexectomy without apparent ill effects. It is quite possible, however, that this pumping action is the important factor in the development of the subarachnoid pathways and in maintaining an open aqueduct of Sylvius during early life.

Weed,[15] in his study of the embryology of the subarachnoid pathways, has shown that the opening of the subarachnoid space coincides with the development of the choroid plexuses and that this space enlarges as the choroid plexuses grow. He seriously questions whether the immature choroid plexus could produce the fluid required to open and maintain the arachnoid pathways, and he suggests that increased intraventricular pressure might cause it. However, he offers no explanation for the increase in intraventricular pressure. This question can be satisfactorily resolved by the present observations on the pulse pressure and pumping action imparted to the CSF by the choroid plexus. These functions of the choroid plexuses provide a mechanism whereby the intraventricular pressure would be raised and CSF actively forced into the arachnoid. As the plexuses grow and increase in power, the CSF is forced out farther and farther into the arachnoid, causing the observed expansion of these spaces.

It is interesting to speculate on the fact that those regions where the neural canal is

almost obliterated contain no choroid plexus. These regions are the central canal of the spinal cord and, occasionally, the aqueduct of Sylvius. In the normal course of growth the ventricles are subjected to the continual CSF pulse and probably expand until the brain and surrounding structures can resist it. The CSF, being constantly forced through the aqueduct of Sylvius, keeps it open. The exits from the fourth ventricle to the arachnoid spaces allow the fluid to escape, thus removing the pressure from the central canal of the spinal cord, so that it does not enlarge.

It is possible, also, in the absence of a sufficiently large choroid plexus pulsation, that there is not enough internal pressure to keep the aqueduct of Sylvius or the subarachnoid pathways open. In the case of the aqueduct closure the pressure would build up from the accumulation of CSF in the lateral and third ventricles, possibly forcing a partial opening of the aqueduct. This escape of fluid would reduce the pressure, allowing the aqueduct to close again. The end-result of such a repeated partial opening and closing of the aqueduct might well be the "forked" aqueduct described by Russell[10] and the hydrocephalic child with occluded aqueduct and absence of choroid plexuses reported by Hassin.[8]

It has been shown (Fig. 4) that the CSF pulse increases with growth. This suggests a new explanation for the ventricular enlargement seen with hypertrophy of the choroid plexuses or with papillomata of the choroid plexus. Here, the mass and the pulsating area of the choroid plexus increase remarkably, and so the intraventricular pulsations would also be expected to increase. This increase in the intraventricular pulse pressure would raise the mean pressure throughout the ventricular system, eventually causing ventricular enlargement without requiring any variation in cerebrospinal fluid production or flow. It has always been assumed in the past that such increased intracranial pressure and dilatation of the ventricular system in the presence of a choroid plexus hypertrophy or papilloma was caused by the increased formation of cerebrospinal fluid. However, in no case have any data been reported on the actual rate of accumulation of CSF, either before or after removal of the tumor mass.

Reduction in the size of the choroid should, by this reasoning, cause a drop in pressure. The effect of plexectomy has been measured in normal dogs and in hydrocephalic dogs (Table). It is entirely possible that the drop in mean pressure afforded by choroid plexectomy is a factor in the success of choroid plexectomy in the treatment of hydrocephalus. It could also account for the spontaneous intracranial hypotension with choroid plexus sclerosis reported by Peuch and associates.[12]

SUMMARY

The choroid plexuses of the cerebral ventricles are the chief sites of transfer of the arterial pulsation to the cerebrospinal fluid.

Each pulse sets up a pressure gradient throughout the CSF system which tends to force CSF out of the cerebral ventricles. This acts as an unvalved pulse pump, imparting a to-and-fro motion to the CSF, the net flow being dependent upon the amount of CSF removed from the subarachnoid pathways.

This pump-like action probably has as its major function the embryonic development of the subarachnoid pathways.

The CSF pulsation contributes a small increment to the intracranial pressure. Under certain pathological conditions, such as hypertrophy or tumors of the choroid plexus, it may become the major source of the increased intracranial pressure.

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RECURRENT CEREBRAL EMBOLISM

A Cause of Chronic Organic Brain Disease

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THE TERM "cerebral embolism" has in the course of time acquired a fixed clinical meaning; in its usual connotation this diagnosis portrays an episode of sudden onset, often of rapid fatal termination. This conception of embolic disease of the brain, although deeply rooted in medical thinking, is inadequate. There is mounting indication that often cerebral embolism does not manifest itself as an acute process; this syndrome may, in fact, pursue a subtle, recurrent chronic course ultimately leading to progressive crippling of cerebral function.

Cerebral embolism is usually thought of clinically as an acute catastrophic neurological complication occurring in patients with known active cardiac disease. All too familiar is the clinical picture of acute cerebral embolism: A patient with known myocardial infarction, convalescing favorably, is suddenly rendered hemiplegic. However, in some instances the onset of symptoms is insidious and slow. In patients who prove to have cerebral embolism often the cardiac disease is not evident during life; rapid development of cerebral symptoms does not occur. Emboli are often minute; the related cerebral infarcts, small and often located in "silent areas" of the brain, may evoke few immediate symptoms. Such embolization tends to be recurrent and by its composite effect may lead to progressive cerebral deterioration, often protracted over a period of years.

Cerebral embolism is a pathologic complex made up of two components: cardiac and cerebral. Coexistent diseases of the heart and nervous system must be recognized in order to identify the syndrome of cerebral embolism.

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CARDIAC ASPECTS OF CEREBRAL EMBOLISM

Because of its role as a complication of heart disease, cerebral embolism has in the past been studied almost exclusively as a problem in cardiology. As a consequence of this approach, the study and evaluation of its neurologic aspects, particularly the chronic effect of cerebral embolism, have been forfeited. The cardiac factors in this syndrome, however, have been investigated in some detail.

Thrombi in the left side of the heart are the prime cause of cerebral embolism; such thrombi are common; their formation sets the stage for the process of systemic embolization. Many types of cardiac disease are associated with intracardiac thromboses. In addition to myocardial infarction, chronic rheumatic heart disease, and endocarditis, intracardiac thrombosis may appear in hypertensive heart disease and in congenital heart disease; it is particularly prone to occur in cardiac disease complicated clinically by fibrillation. In a study of 6,285 consecutive autopsies, Garvin [1] found mural thrombi present in the heart in 4.2% of all cases; in 771 consecutive autopsies on adults who died of heart disease, intracardiac thrombi were present in 34.4%.

Coronary occlusion with myocardial infarction is the commonest cardiac disorder associated with the formation of intracardiac thromboses. The endocardial aspect of the infarcted portion of the ventricle becomes coated with a mural thrombus; Garvin [1] found intracardiac mural thrombi in 66.9% of cases of coronary artery disease with myocardial infarction. Levine [2] stresses the fact

that mural thrombi may remain pocketed in the ventricles of the heart for many years. Poised and threatening, these thrombi provide a constant source of emboli ready to be ejected and distributed through the body at any time.

Hyman and Parsonnet [3] point out that a long interval may elapse between the time of a myocardial infarction and an embolic attack. They cite two such cases of delayed cerebral embolism. In one case, a 65-year-old woman who had survived a coronary thrombosis five years previously and had enjoyed relatively good health suddenly suffered a hemiplegia; autopsy showed that an embolus arising from an intracardiac mural thrombus had lodged in the basilar artery of the brain. The second case was that of a 55-year-old man with a history of repeated attacks of coronary disease, but relatively well in the last three years, who suddenly became comatose and died; a cerebral embolus was demonstrated at autopsy.

Coronary disease, since it is the most frequent cause of intracardiac thrombosis, plays a prime role in igniting the chain of phenomena leading to cerebral embolism. Connor and Holt [4] noted evidence of cerebral embolism in 5% of patients with coronary thrombosis. The symptoms of hemiplegia, aphasia, convulsions, and psychosis, climaxing the clinical course of a patient with recent myocardial infarction, are easily recognized manifestations of cerebral embolism. In such patients embolic involvement of the kidneys, intestine, spleen, and other organs may occur; hematuria, melena, abdominal pain, and other symptoms of visceral infarction appearing clinically tend to confirm the embolic genesis of the concurrent central nervous system symptoms.

Rheumatic heart disease is the second most important cause of intracardiac thrombosis and cerebral embolism. As a late effect of rheumatic heart disease, mitral stenosis with great dilatation of the left atrium occurs. With atrial fibrillation, which almost always accompanies mitral stenosis, there is stagnation of blood flow in the dilated chamber; thrombi form. Garvin [1] found mural thrombi in the left side of the heart in 19% of cases of rheumatic heart disease; the incidence of thrombi in this group was particularly high in the older age group and in cases of fibrillation; embolization often occurred many decades after the original acute rheumatic attack. Harris and Levine [5] studied 88 cases of mitral stenosis in which there was evidence of cerebral embolism; the clinical diagnosis of cerebral embolism was based upon the sudden appearance of paralysis in these cases. As noted by these authors, "The typical case was one in which paralysis occurred suddenly at a time when there was no complaint of dyspnea." In approximately 25% of the cases the embolic episode was rapidly fatal and was confirmed at autopsy. Of the nonfatal cases, approximately one-third appeared to recover completely from the effects of the embolism; the remainder showed varying degrees of persisting embarrassment of nervous system function. Friedberg [6] stresses the recurrent nature of cerebral embolism in mitral stenosis. The occlusion of a small cerebral artery may escape immediate consideration, but it may be the prelude to future chronic neuropsychiatric disability. Foley and Wright [7] noted the chronic persistence of mental changes after cerebral embolism in mitral stenosis.

In bacterial endocarditis, Toone [8] and others point out that major neurological symptoms appear in approximately one-fourth of cases; patients may develop embolic lesions early in the course of the disease and present hemiplegia, brain tumor symptoms, or mental changes. Parenthetically, the current use of antibiotics in arresting the course of bacterial endocarditis makes the matter of irreversible embolic damage to the brain a problem of increasing importance.

Thrombotic nonbacterial endocarditis has received increasing attention in recent decades.* This is a degenerative valvular disease, appearing in debilitated persons, in which thrombotic vegetations are engrafted on the cardiac valves; these verrucae are usu-

* References 9, 10, and 11.

ally minute, but occasionally there are formed soft, friable deposits 10 to 20 mm. in diameter, which resemble the vegetations of bacterial endocarditis. In recent years an apparent increased incidence of thrombotic nonbacterial endocarditis, attributed largely to the use of antibiotics, has been reported.[10] As observed by Allen and Sirota,[11] the larger verrucae are loosely attached to the valve and are prone to produce emboli; these investigators noted that infarcts, and even fatal encephalomalacia, may result.

NEUROLOGICAL ASPECTS OF RECURRENT CEREBRAL EMBOLISM

As viewed in the literature, the syndrome of cerebral embolism is generally conceded to the province of cardiovascular pathology. There are but few neuropsychiatric references dealing with embolic disease of the brain. This seems paradoxical. Considering the profound acute and chronic effects suffered by the end-organ, the brain, it is surprising that the syndrome of cerebral embolism has not evoked greater interest in the literature of neurology and psychiatry.

Though observed by the cardiologist, chronic recurrent pattern of cerebral embolism has rarely been described from a neurologic point of view. Heathfield and Jewesburg [12] describe repeated neurologic and psychotic reactions due to recurrent cerebral embolism in three patients with mitral stenosis. Manguel [13] describes a 50-year-old patient with chronic rheumatic mitral disease who in late life showed episodic neurologic complications; the patient developed Jacksonian seizures. Hemiplegia occurred. Progressive bradyphrenia was evident. Finally there was a sudden onset of coma. These neurologic complications were thought to be of multiple embolic origin. Mezei [14] recognizes that a small group of cases of Parkinsonism is due to embolism and cites an example: The patient, a 32-year-old woman, developed rapidly progressing symptoms of Parkinsonism and schizophrenia during the last six months of life. Autopsy revealed mitral stenosis and mural thrombi in the left atrium. The brain showed multiple small infarcts in the caudate and lentiform nuclei and occipital area of the cerebrum. In addition, there were renal infarction and beginning gangrene of the leg. It was thought that, although undiagnosed during life, the cardiac disease was responsible for the central nervous system lesions. The cerebral and other visceral infarcts were interpreted as embolic in origin. Thompson [15] reports six cases with cerebellar lesions interpreted as embolic in origin. Leavitt [16] cites the case of a 43-year-old woman who, as the result of multiple cerebral emboli, showed progressive mental and neurologic deterioration during the course of several years.

TABLE 1.—*Syndrome of Recurrent Cerebral Embolism*

Age at onset	Relatively young or middle-aged adult
Neurologic history	Repeated "small strokes"; progressive deterioration
Cardiac history	Remote myocardial infarction or old rheumatic heart disease
Usual antemortem clinical diagnosis	Cerebral arteriosclerosis
Heart: autopsy	Heart with old myocardial infarction or mitral stenosis; intracardiac thrombosis
Other viscera: autopsy	Multiple visceral infarcts: spleen, kidney
Brain: autopsy	Multiple infarcts of varying size and age; embolic occlusion of arteries; arteriosclerosis absent or minimal

Acute cerebral embolism, that which complicates the convalescence of patients with recent myocardial infarction, is in most instances clearly appraised in general medical practice. Recurrent cerebral embolism, however, with its piecemeal destruction of the brain, is a problem which has received relatively little clinical consideration. There is a general unawareness of the frequency with which embolic brain disease of a chronic nature may develop in the wake of chronic cardiac disease. There is, however, increasing evidence to indicate that recurrent cerebral

embolism, mimicked and disguised, is of considerably wider incidence than is generally realized. Nonfatal cerebral embolism may, in fact, represent one of the most important causes of chronic organic brain disease.

CRITERIA FOR EVALUATING THE INCIDENCE OF RECURRENT CEREBRAL EMBOLISM

The diagnosis of recurrent cerebral embolism is based upon distinctive changes (1) in the heart and (2) in the brain (Table 1). The morphologic criteria must in each case be correlated with the clinical background. In its classic form the clinical syndrome of recurrent cerebral embolism is characteristic. There is usually a background of protracted heart disease; neurologic symptoms commonly appear in the fourth or fifth decade. The course is punctuated by sharp episodes of new and recurrent neurologic symptoms which gradually lead to chronic central nervous system deterioration. At autopsy, typically, there is chronic cardiac disease with mural thrombi in the left side of the heart. The brain shows focal infarcts of varying ages. The main arteries of the brain are generally free of arteriosclerosis. In the region of the infarction, arterial occlusion related to embolism may be demonstrable.

The cardiac changes in recurrent cerebral embolism are necessarily chronic in nature. The source of the embolism must be identified; the most frequent site of origin is a mural thrombus in the left ventricle. In the characteristic instance, in association with myocardial infarction, the thinned, fibrotic ventricle wall tends to form an aneurysmal pocket (Fig. 17); in this recess partially organized thrombus is cached; lodged here for many years, the deep portion of the thrombus may become calcified; the ragged, friable surface of the thrombus may, from time to time, discharge embolic fragments into the arterial circulation. In chronic rheumatic heart disease and other cardiac disorders, particularly with fibrillation, emboli arise from thrombi in the diluted left atrium. In cases of endocarditis, emboli arise from valvular vegetations.

Cerebral lesions produced by recurrent embolism are generally distinctive. Multiple infarcts of varying age are the typical feature in the cerebral pathology of this syndrome. The multiplicity of brain lesions reflects the assault by showers of emboli and is responsible for the plethora of neuropsychiatric symptoms. The varying ages of the infarcts echo the cyclic, episodic pattern of embolization; the location and age of the infarcts can, in retrospect, be correlated with the succession of symptoms as they punctuated the clinical course of the patient during life.

In classic cases of recurrent cerebral embolism the arteries of the brain are thin-walled and pliable and show little or no arteriosclerosis. The presence in the brain of severe arteriosclerosis with luminal occlusion tends to contravene the diagnosis of cerebral embolism, since the process of sclerosis may *pari passu* be the cause of multiple cerebral infarctions.

In the region of embolic infarction it is often possible to demonstrate occlusion of arteries by antemortem clot in varying stages of organization. It is likely that emboli, arising from mural thrombi in the heart, after impaction in a cerebral artery, frequently increase in extent by the process of appositional thrombosis. In this manner, more and more of the adjoining arterial tree becomes occluded; consequently, there is progressive local destruction of brain substance with consequent parallel neuropsychiatric deterioration clinically. The presence of multiple infarcts in the kidney, spleen, or other viscera lends support to the diagnosis of embolic disease of the brain.

All of the clinical and morphologic features noted above can be clearly delineated in most cases of recurrent cerebral embolism. Certain facets of the picture may, in some instances, be incomplete. Heart disease, although present, may escape diagnosis clinically. Or, in cases of remote myocardial infarction, mural thrombi, present in the past, may not be evident at the time of autopsy. It is recognized that the absence of thrombi at autopsy does not preclude the possibility of

their previous existence and dislodgment during life.[17] Although they may remain in the heart for long periods, thrombi may, on the other hand, through proteolytic enzyme action undergo gradual dissolution; in addition, fragments of the friable thrombus, detached from time to time, may be distributed as emboli to the brain or other viscera. Eventually, through the process of dissolution and embolization, the original thrombotic mass in the heart may become completely dissipated.

In some instances chronic organic brain disease of many years' duration may be embolic in genesis, but not demonstrably recurrent; at gross autopsy only a single gross cerebral infarct may be present; however, additional smaller infarcts are usually demonstrable microscopically.

Recurrent cerebral embolism, though by nature a chronic process, may, however, manifest a relatively subacute course; clinically such patients may be institutionalized because of a rapidly developing psychotic reaction; they present neurologic and psychotic symptoms of sudden onset and rapid progression over a period of weeks or months.

In order that the incidence of cerebral embolism may be ascertained, three conditions must be fulfilled: 1. The evaluation must be based on autopsy studies. 2. All or a high per cent of deaths in a given community must be examined. 3. The examination of the brain must be closely correlated with the autopsy findings in other organs.

Autopsy offers the only valid basis for estimating the incidence of a clinically deceptive process such as cerebral embolism. Clinical studies afford only a presumptive basis for estimating the occurrence of cerebral embolism. Obvious instances of acute cerebral embolism, appearing in patients with recent myocardial infarction, offer no diagnostic problem at the bedside. However, in more equivocal circumstances, cases in which the antecedent heart disease is not evident, or cases in which the effects produced by the emboli are delayed, the clinical diagnosis of cerebral embolism is often artlessly missed. Only by postmortem examination in a high per cent of deaths can the actual incidence of cerebral embolism be brought to light.

In a study of cerebral embolism, changes in the brain observed at autopsy must be carefully correlated with findings in the heart and other viscera. In many institutions the general autopsy is performed by the staff pathologist and the study of the brain is completed by the neuropathologist, usually at a later date, often in an institute removed from the general pathology department. With such a system it may become difficult to appreciate certain organic relationships in a given case. Even though autopsy and brain examination be performed with vigilance and thoroughness, this dissociation in the postmortem procedure invites the hazard of correlative omission and misinterpretation. In autopsies of older subjects many incidental findings, appearing unimportant, may be observed; consequently, the presence of a small mural thrombus in the left ventricle may not be included in the protocol summary or may not be brought to the attention of the neuropathologist in the review of the case at the time of brain cutting. As a result, in such cases, albeit numerous focal infarcts are obvious when the brain is examined, the diagnosis of embolic infarction may escape consideration.

To obtain a valid estimate of the incidence of cerebral embolism a complete postmortem examination should be performed in all cases, particularly in the presence of heart disease. At autopsy, with the finding of myocardial infarction or mitral stenosis, the brain must be examined with great care. Often, when the heart shows a myocardial infarction which tends to explain the cause of death, opening of the cranial cavity is considered superfluous labor and is omitted. On the other hand, in cases having clinically an overwhelming neurologic basis for the cause of death, necropsy is sometimes curtailed to an examination of the brain; the cardiac origin of cerebral lesions may consequently escape definition.

In the study of thromboembolic disease it is requisite that necropsy be performed on

bodies unembalmed. The problem of analyzing blood clots at autopsy is considerably complicated by embalming; arterial irrigation may distort and disguise thrombi, particularly within the heart. The stream of embalming fluid, introduced under pressure, may bring about artifactual dislodgment or impaction of intracardiac or intravascular clots. The embalming solution may convert a simple postmortem clot to a mottled gray-red, friable mass resembling a thrombus; on the other hand, a bona fide thrombus may be so altered that its true nature at autopsy remains a matter of doubt.

For a comprehensive appraisal of the incidence of cerebral embolism, postmortem examination must be performed in all or a high percentage of deaths in a given community. Estimation of the incidence of cerebral embolism should, as nearly as possible, be based on a cross-sectional study of fatal illness in the population at large and not merely on selected cases. There is a natural tendency in many hospitals to seek autopsy information only in cases of special academic interest. Lacking necropsy confirmation, hemiplegia, psychosis, and other prosaic central nervous system symptoms, particularly in older patients, are often categorically ascribed to cerebral hemorrhage or arteriosclerosis. Herein lies the source of wide error. Autopsy statistics obtained from general hospitals tend to be misleading because of the selectivity of admissions. Patients with chronic neurologic disorders often do not seek admission terminally.

For evaluation of the incidence of cerebral embolism, the study must be of appropriate proportions and must extend over a period of years.

It is evident that optimal circumstances for the study of cerebral embolism are not often available. The presence of cerebral embolism frequently evades detection, even by autopsy. Considering the technical difficulties and variabilities that arise in its evaluation, it becomes understandable why the incidence of cerebral embolic disease has remained a matter of obscurity.

INVESTIGATIVE PROCEDURE

Attention became focused on the problem of recurrent cerebral embolism in the present study because of the unheralded incidence of this syndrome uncovered at autopsy. This investigation was carried out in the large institutionalized population of Columbus State Hospital, Columbus, Ohio, during the period from Sept. 1, 1949, to March 1, 1954. This study was formulated originally to define the nature and incidence of organic brain disease occurring in this population; at an early date the unexpected frequency of recurrent cerebral embolism proved to be a most significant aspect of the data. An evaluation of the occurrence of this syndrome forms the basis of the present study.

Optimal clinical and autopsy facilities were present to implement this investigation. Autopsy information was available in a high percentage of deaths occurring in this large institutionalized population over a long period of time. The population studied was equivalent to a community of approximately 2,500 people. In this state institution, maintained for the treatment of neuropsychiatric disease, all adult age ranges are present in the census. The population is composed in large measure of persons who, lacking family ties and suffering from the mental and physical infirmities of declining years, require simple maintenance and custodial care. The ages at death ranged from 22 to 94 years; most deaths, as in any community, were in adults of advanced years. The age distribution of the cases in this autopsy series was appraised by comparing the age groups here with the age pattern in the adult mortality statistics in the surrounding city of Columbus, Ohio, for the year 1951. The distribution by ages in the two populations compared proved to be strikingly parallel. The age group from 20 to 40 years formed 5.7% of the deaths in this study and 6.0% of the deaths noted in the city statistics; from 40 to 60 years the respective distribution was 21.6% and 24.9%; for 60 years and over, the distribution was 72.7% and 69.1%. Accordingly, it is evident that the autopsy series reflects closely the age distribution of adult deaths

occurring in the general population in this region.

During the period of this study 922 institutional deaths occurred. Of these, 538, or 58% of the deaths, were studied at autopsy. Examination of the cranial contents was permitted in 525 of the autopsies.

In formulating this investigation two principles were emphasized: First, in order to obtain valid cross-sectional data regarding the incidence of disease, effort was made uniformly to obtain autopsy permission in each death regardless of the immediate academic interest in the case.

Second, the postmortem routine was standardized. In evaluating thromboembolic disease, necropsy must be done not only in a high percentage of cases, but in a carefully regulated, vigilant manner; technical procedures must be carefully controlled. To avoid artifacts induced by postmortem autolysis and embalming, as nearly as possible, autopsies were performed directly after death. In 65% of cases autopsy was done within five hours after death; in 95% of cases postmortem examination was done before embalming. Eighty-eight per cent of the autopsies were performed by me. In order to maintain close correlation of the clinical data and general autopsy findings, all brains, after 7 to 10 days' fixation in formalin, were sectioned by me in the presence of the clinical staff.

INVESTIGATIVE RESULTS

Of the 525 brains examined consecutively in this study, 371 showed a significant degree of chronic organic brain disease; in the preponderance of these cases the essential pathologic changes were those of senile encephalopathy and cerebral arteriosclerosis. In the remaining group, of 154 cases, composed largely of patients institutionalized with nonorganic psychoses, demonstrable cerebral lesions were not present at death.

Seventeen cases of recurrent cerebral embolism were identified; in this institution 4.6% of patients with chronic organic brain disease who died and were autopsied had cerebral infarcts due to recurrent embolization. These data signify that, considering organic and nonorganic disease, approximately 1 in 30 patients committed to this institution showed at autopsy cerebral embolism as the basis for his chronic neuropsychiatric disease.

In evaluation of recurrent cerebral embolism, the extent of incidence was evident by comparing its frequency with other types of chronic organic brain disease. Embolic disease of the brain proved to be of greater importance as a cause of chronic neuropsychiatric disease than processes such as trauma or tumor growth. Syphilis, generally regarded as a widespread cause of organic brain disease, was observed in 47 instances in this autopsy series; accordingly, it will be noted that recurrent cerebral embolism appeared approximately one-third as often as dementia paralytica in the population studied here.

In addition to the 17 manifest cases, there were 9 other instances in which the diagnosis of recurrent cerebral embolism strongly suggested itself; however, these cases were considered equivocal because in each instance certain features pertinent to the diagnosis were incomplete. Accordingly, in these cases a definite pathologic diagnosis of embolism was withheld; these cases were not considered further in the present evaluation.

In some cases the brain at autopsy showed, in addition to the embolic infarcts, changes of senile encephalopathy or arteriosclerosis of moderate extent; in such instances, with a history of sudden onset of neurologic symptoms and autopsy findings of mural thrombus in the left side of the heart, as well as focal infarcts in the brain, an embolic process was clearly dominant.

As is shown in Table 2, recurrent cerebral embolism in this study was associated with three types of heart disease: myocardial infarction, old rheumatic heart disease, and thrombotic nonbacterial endocarditis. There were 11 cases of recurrent cerebral embolism in patients having old myocardial infarction and harboring intracardiac mural thrombi; hypertension was usually present.

CASE 1 (Autopsy 10459; man, 67 years).—This patient had a myocardial infarction, diagnosed

TABLE 2.—*Recurrent Cerebral Embolism; Clinicopathologic*

Cardiac Group	Case No.	Autopsy No.	Age, Yr.	Sex	Autopsy Findings: Heart Lesions	Brain Lesions: Principal Infarcts	Brain Lesions: Arteriosclerosis	Other Organ Infarcts
Myocardial infarction; hypertension	1	10459	67	M	Old and recent myocardial infarction; mural thrombi in left ventricle	Corpus striatum; internal capsule	Minimal	Kidney
	2	10421	70	M	Old myocardial infarction; mural thrombus in left ventricle	Temporal, 3 cm.; frontal, 7 cm.; old	Minimal	.....
	3	10691	45	F	Old and recent myocardial infarction; mural thrombi in left ventricle	Multiple, varying size and age	Minimal	Spleen
	4	10715	42	F	Old and recent myocardial infarction; mural thrombi in left ventricle	Frontal, 4 cm.; parietal, 12 cm.; old and recent	Minimal	Spleen
	5	10509	70	M	Old and recent myocardial infarction; mural thrombus left ventricle	Subacute; posterior, frontal, and parietal; 3 cm.	Minimal	.....
	6	10155	42	M	Old myocardial infarction; mural thrombi in left and right atria	Multiple, varying age; largest, right frontal, 6 cm.	Minimal	.....
	7	10210	82	F	Mural thrombi in left and right atria	Corpus striatum, 3 cm.; old	Moderate	Spleen
	8	9968	76	M	Old and recent myocardial infarction; mural thrombus left ventricle	Multiple; varying age; largest, 3 cm., occipital lobe	Moderate	.....
	9	10392	47	M	Old myocardial infarction; mural thrombi in left ventricle	Multiple; largest 8 cm., parietal; old	Moderate	.....
	10	10170	48	M	Old myocardial infarction; mural thrombus in left ventricle	Frontoparietal, 8 cm.; subacute	Minimal	.....
	11	10665	76	F	Old and recent myocardial infarction; mural thrombus in left ventricle	Multiple, up to 2 cm.; old	Moderate	Spleen; kidney; intestine
Rheumatic heart disease	12	10800	40	F	Mitral stenosis; mural thrombus in left atria	Multiple; varying age; largest, 3 cm., occipital lobe	Moderate	.....
	13	10172	63	M	Mitral stenosis	Multiple; largest, 4 cm.; varying age	Minimal	Spleen
	14	9619	78	F	Mitral stenosis; mural thrombus in left ventricle	Multiple; varying size	Minimal	Intestine
	15	10482	53	F	Mitral stenosis	Cerebellar, 4 cm.; old	Minimal	.....
	16	10498	79	M	Mitral stenosis; mural thrombus in left atrium	Multiple; largest, left parietal, 4 cm.; varying age	Moderate	.....
Nonthrombotic bacterial endocarditis	17	10590	79	F	Large thrombi on mitral leaflets	1.5 cm.; old; parietal	Minimal	.....

clinically at the age of 57; one year later he suddenly became hemiplegic and developed speech difficulty. A second stroke occurred at the age of 62. Five months before death there was sudden onset of convulsions, followed by coma; subsequently, there were recurrent epileptiform seizures. At autopsy the heart showed an old infarct in the left ventricle; pocketed in the apex of the ventricle was a mural thrombus 1.0 cm. wide (Fig. 1). In the brain there was a 2 by 3 cm. area of old necrosis in the region of the left corpus striatum; smaller lesions were scattered through the cerebrum (Fig. 2). The cerebral arteries were free of sclerosis; in the area of infarction arterial lumina contained emboli (Fig. 3).

Clinically, this case presents the classic cardiac and neurologic features of recurrent cerebral embolism. The recurrent nature of the embolic process is amply represented in the clinical course and in the autopsy findings in the brain.

CASE 2 (Autopsy 10421; man, 70 years).—This patient had a "stroke" at the age of 59. No significant cardiac disease was recognized clinically. There was a gradual progression of mental changes with increasing speech difficulty. At the age of 67 and 69 there were recurrent apoplectiform seizures. The final ictus rendered the patient mentally confused and incoherent. At autopsy the heart showed an extensive left ventricular and septal infarct with a 2 cm. mural thrombus tightly adherent to the intima (Fig. 4). In the brain there were multiple old infarcts distributed through the cerebral cortex

Analysis of Seventeen Cases With Autopsy

Clinical Correlation						
Cardiac Disease			Neuropsychiatric Disease			
Antemortem Diagnosis	Signs and Symptoms	Known Duration, Yr.	Antemortem Diagnosis	Signs and Symptoms	Age at Onset, Yr.	Duration
Hypertension; arteriosclerosis	Moderate hypertension	10	Cerebral arteriosclerosis	Sudden onset; hemiplegia; 4 neurologic attacks	58	9 yr.
Not diagnosed	None	..	Cerebral arteriosclerosis	Three distinct "strokes"	59	11 yr.
Hypertensive arteriosclerosis	Moderate hypertension; cardiac decompensation	?	Schizophrenia	Rapid progression of mental changes during last 2 yr. of life	43	2 yr.
Hypertensive arteriosclerosis	"Heart attacks"	10	Schizophrenia; cerebral embolism	Two ictuses; hemiplegia; rapid progression of psychosis after embolism	41	1 yr.
Hypertensive arteriosclerosis	Slight decompensation	4	Cerebral arteriosclerosis	Two sudden attacks; gradual mental changes; hemiplegia	66	4 yr.
Rheumatic and arteriosclerotic heart disease	Fibrillation; decompensation	?	Cerebral thrombosis; CNS syphilis	"Stroke" with slight hemiplegia; progressive dementia	42	2 mo.
Arteriosclerosis	Fibrillation	6	Cerebral arteriosclerosis	Hemiplegia; progressive mental deterioration	76	6 yr.
Hypertensive arteriosclerosis	Hypertension; fibrillation; decompensation	?	Cerebral arteriosclerosis	Three neurologic attacks; aphasia; hemiplegia	74	2 yr.
Hypertensive arteriosclerosis	Slight hypertension	?	Syphilis	Sudden hemiplegia; two ictuses; gradual dementia	37	10 yr.
Arteriosclerosis	Repeated "heart attacks"; cardiac decompensation	8	Cerebral arteriosclerosis	Sudden onset; aphasia; later hemiplegia	48	4 wk.
Hypertensive arteriosclerosis	Moderate hypertension; "heart attacks"	2	Senile psychosis	Sharp onset, hemiplegia; mental deterioration	72	4 yr.
Hypertensive arteriosclerosis	Hypertension; fibrillation; decompensation	?	Cerebral arteriosclerosis	Three neurologic attacks; aphasia; hemiplegia	74	2 yr.
Arteriosclerosis	Fibrillation	4	Cerebral arteriosclerosis	Multiple seizures during childhood	53	10 yr.
Type not diagnosed	Course asymptomatic	?	Manic-depressive psychosis	Rapid mental deterioration	72	6 mo.
Rheumatic	Fibrillation; decompensation	47	Paranoid	Transient hemiplegia; gradual progression of mental changes	43	10 yr.
Type not diagnosed	Fibrillation; decompensation	25	Manic-depressive psychosis	Convulsive seizures in late years; mental deterioration	49	30 yr.
Type not diagnosed	None	..	Cerebral arteriosclerosis	Rapid onset of mental symptoms	78	1 yr.

(Fig 5). Histologically there were wide areas of old encephalomalacia; there was little arteriosclerosis (Fig. 6).

Although this patient suffered a severe myocardial infarction at a remote time prior to death, this cardiac disease was apparently silent clinically. The multiple infarcts in the brain found at autopsy accurately reflect the history of three distinct ictuses recorded clinically. This case clearly illustrates the difficulty in recognizing the syndrome of recurrent cerebral embolism when the cardiac component is not evident clinically.

CASE 3 (Autopsy 10691; woman, 45 years).—The patient, known to have hypertension of many years' duration, showed electrocardiographic changes of myocardial infarction; concurrently she developed mental changes diagnosed clinically as schizophrenia. At autopsy myocardial infarcts, old and recent, were present; large, ragged thrombi were present in the left ventricle (Fig. 7); some of the thrombi were tightly adherent, and others were friable and loose (Fig. 8). Infarction was present in the spleen, as well as the brain.

In this case the symptoms of schizophrenia were apparently increased by the chronic organic damage incited in the brain by the embolic process.

CASE 4 (Autopsy 10715; woman, 42 years).—At the age of 32 a clinical diagnosis of myocardial infarction was established. At this time there were visual defects and noticeable mental changes. A diagnosis of schizophrenia was considered clinically.

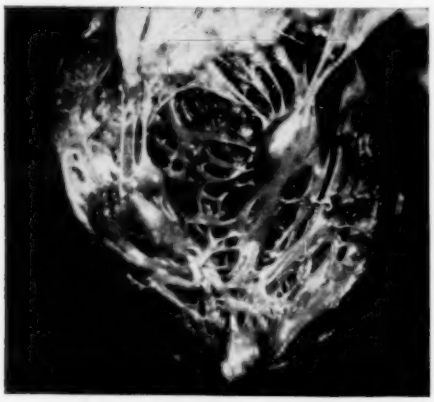


Fig. 1 (Case 1).—Heart with old myocardial infarction at the apex of the left ventricle. The thinned ventricle wall forms an aneurysmal recess harboring a thrombus.

At the age of 41 the patient had a sudden onset of hemiplegia; this attack was diagnosed as cerebral embolism clinically. Ten months before death the patient was found in a dazed, blinded, confused state. At autopsy the clinical diagnosis of cerebral embolism was confirmed. There was an old myocardial infarction and an adherent 8 by 4 by 2 cm. thrombus in the left ventricle (Fig 9). The spleen

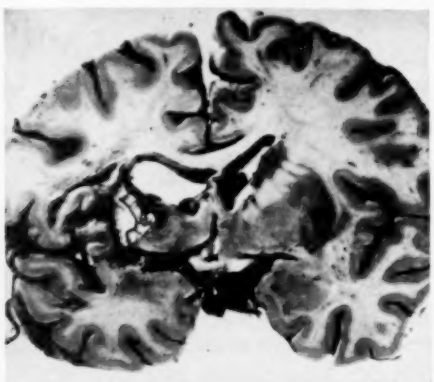


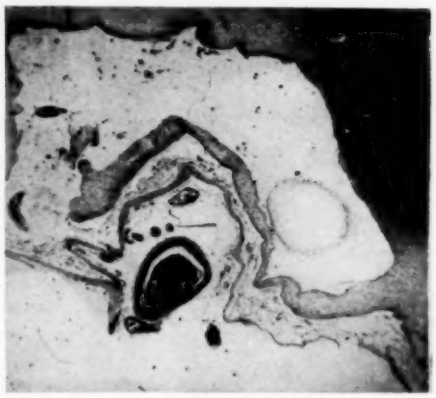
Fig. 2 (Case 1).—Ancient infarct in the left corpus striatum associated with remote cerebral emoblism.

(Fig. 10) and brain showed infarcts (Figs. 11 and 12). There was no cerebral arteriosclerosis. The lesions in the brain varied from 1.0 to 5 cm. in diameter and were of varying age.

Of the 17 cases of recurrent cerebral embolism in the present study, this was the only one with neuropsychiatric symptoms in which the diagnosis of embolism was established during life. Correlation of the chronic heart and cerebral disease was realized clinically when this cardiac patient became hemiplegic and psychotic one year before death. In this instance, as in Case 3, the schizophrenic endowment of the patient was activated rapidly under the catalytic stimulus of the embolism.

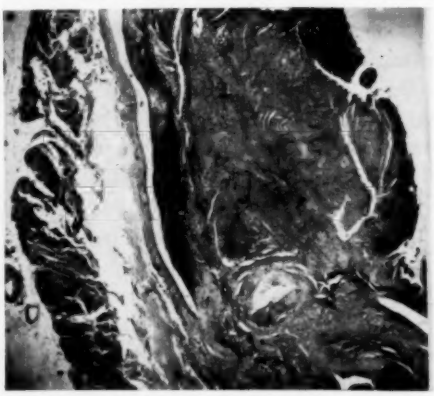
Case 5 (Autopsy 10509; man, 70 years).—The patient had been committed originally as a custodial problem. In this case there was a clear diagnosis

Fig. 3 (Case 1).—Area of remote infarction. Arteries show little sclerosis; lumens contain impacted emboli. Holzer stain; × 10.5.



of myocardial infarction four years before death. Mental deterioration increased after the time of the myocardial infarction. Three years before death there was an episode of coma, attributed to "cerebral spasm" clinically. Five weeks before death the patient awoke with left hemiplegia. At autopsy the heart showed severe coronary sclerosis with thrombosis. There were numerous mural thrombi in the

Fig. 4 (Case 2).—Heart with organizing mural thrombus attached to ventricle wall. Eosin-hematoxylin stain; × 4.



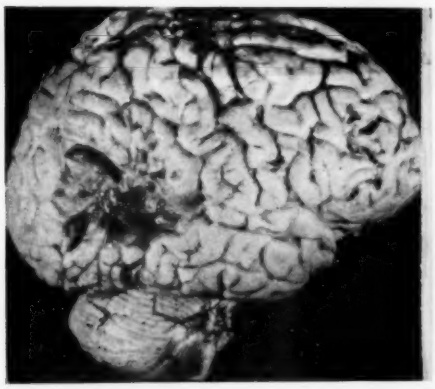


Fig. 5 (Case 2).—Brain showing multiple infarctions of the cerebral cortex due to remote emboli.

left ventricle. The brain was free of arteriosclerosis. There was a subacute infarct in the motor area of the right cerebrum.

In this case mural thrombi may have been present for many years in association with the old myocardial infarction and may have been responsible for the syncope and mental deterioration that occurred in the late years of this patient's life.

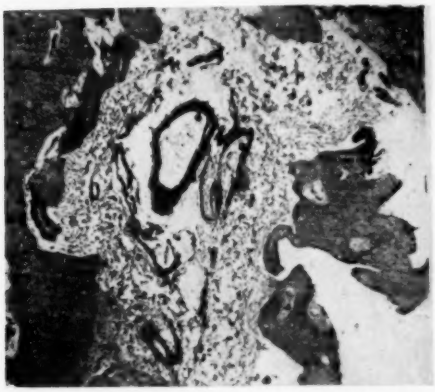
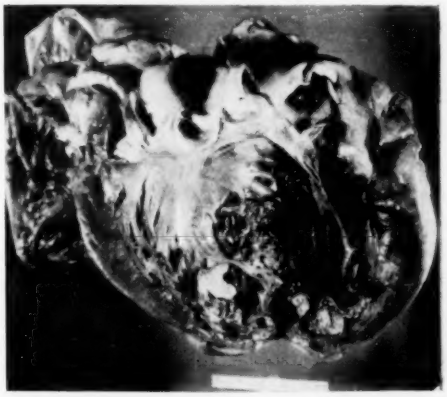


Fig. 6 (Case 2).—Section through the cerebral cortex from principal lesion in Figure 5. Despite the age, 70 years, little arteriosclerosis is present. Holzer stain; × 9.5.

Case 6 (Autopsy 10155; man, 42 years.)—This patient was committed because of gradual onset of mental confusion following a sudden onset of hemiplegia. A diagnosis of old rheumatic heart disease with fibrillation was made clinically. At autopsy, although there was no definite evidence of rheumatic heart disease, an old myocardial infarction was found. Both atria contained friable auricular thrombi, up to 1.5 cm. in diameter. The brain showed multiple old infarcts, up to 5 cm. in width. Pulmonary embolism was present.

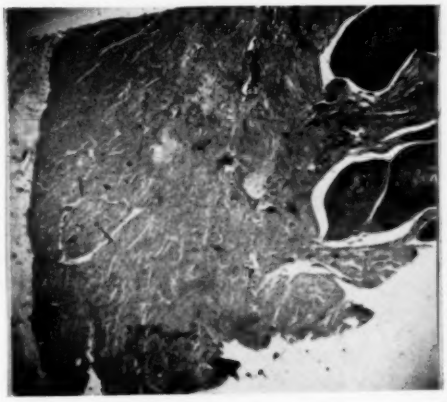
Antecedent cardiac disease, although misdiagnosed, was recognized in this case. It is noteworthy that in this case embolism occurred not only from the left atrium to the brain but also from the right atrium to the lungs.

Fig. 7 (Case 3).—Hypertensive heart disease with progressive myocardial infarction and multiple friable, ragged mural thrombi in the left ventricle giving rise to systemic emboli.



Case 7 (Autopsy 10210; woman, 82 years).—Clinically, there was in this case long-existent cardiac fibrillation. The patient became suddenly hemiplegic five years before death; thereafter she showed progressive disorientation. Autopsy re-

Fig. 8 (Case 3).—Section through mural thrombus in left ventricle shown in Figure 7. Although adherent, the friable texture of the thrombus is evident. Eosin-hematoxylin stain; × 6.



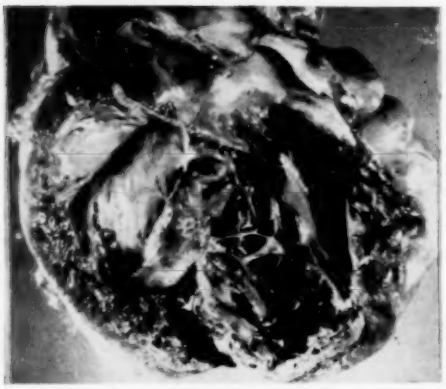


Fig. 9 (Case 4).—Myocardial infarction, of 10 years' duration clinically, in a 42-year-old woman. Large mural thrombus present.

vealed large friable thrombi in both atria and a large cerebral infarction.

The formation of intracardiac thrombi in this patient was apparently related to the long-existent cardiac fibrillation. Although there was some cerebral arteriosclerosis in the brain, the clinical picture of sudden onset

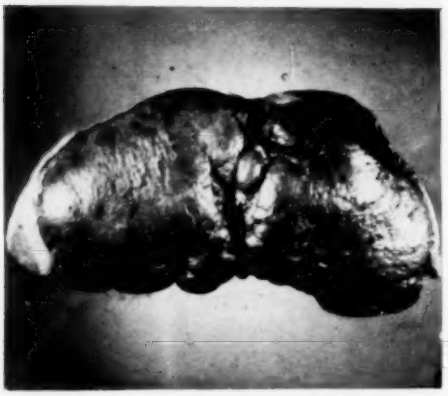
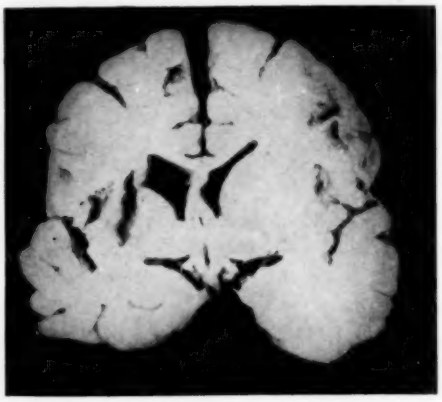


Fig. 10 (Case 4).—Spleen with old infarction due to embolism. Brain also shows infarction (Fig. 11).

of hemiplegia and the disclosure at necropsy of a heart harboring friable mural thrombi support the diagnosis of embolism.

Case 8 (Autopsy 9968; man, 76 years).—This patient was a diabetic known clinically to have a remote myocardial infarction, hypertension, and fibrillation. Ten months before death he experienced a sudden onset of coma, which lasted three days; thereafter he had speech difficulty, noticeable irritability, and disorientation. Seven months before death the patient became suddenly hemiplegic. Terminally he became agitated, then comatose. Autopsy showed old and recent infarcts in the left ventricle. At the apex of the left ventricle there was an adherent, friable mural thrombus (Figs 13 and 14). The arteries at the base of the brain, although thick-walled, showed no significant narrowing of the lumen. The brain showed multiple infarcts of varying age, from 0.5 to 3.0 cm. in diameter (Fig. 15).

Fig. 11 (Case 4).—Multiple infarcts in cerebrum. Major infarction present in right cerebrum; patient hemiplegic.



The multiplicity of clinical neurologic symptoms occurring with sudden onset at varying intervals can be correlated with the presence of the multiple embolic cerebral infarcts of varying age found at autopsy. This case also emphasizes the recurrent

Fig. 12 (Case 4).—Section through infarcted striatal area evident in Figure 11. Hemiplegia present for one year before death. Holzer stain; × 6.

Fig. 13 (Case 8).—Remote myocardial infarction with persisting mural thrombus.

nature of the syndrome which, by additive effect, leads to chronic central nervous system deterioration.

Case 9 (Autopsy 10392; man, 47 years).—This patient had a sudden "stroke" at the age of 37, with hemiplegia and speech difficulty; this was followed by mental changes. No cardiac disease was evident clinically. The patient had been treated for

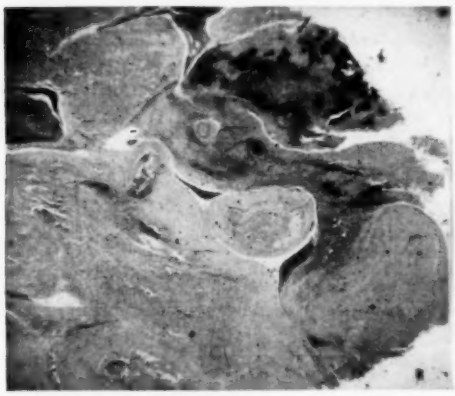
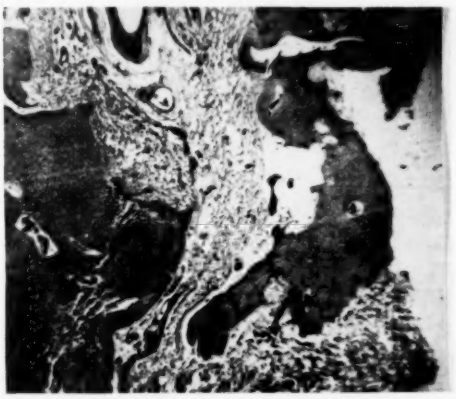


Fig. 14 (Case 8).—Well-organized mural thrombus attached to fibrotic infarction in ventricle wall; Eosin-hematoxylin stain; × 6.

syphilis; blood and spinal fluid serology were negative for syphilis. A week before death he experienced another ictus; there was further impairment of speech and deepening coma. Autopsy disclosed an old coronary thrombosis and myocardial infarction (Figs. 16 and 17). The lower portion of the left ventricle wall, fibrotic and thin, formed a shallow pocket, lodging a mural thrombus. The brain showed a massive pseudoporencephalic defect, 8 by 5 cm., in the left posterior frontal, parietal, and temporal area (Fig. 18). Other old infarcts of smaller extent were also present. The left middle cerebral artery was occluded by hyaline fibrillary material. Grossly, the lumina of other arteries were patent.

In this case, cardiac disease was not noted during life; it is likely that the symptoms were obscured by the overwhelming neurologic disease present in the patient. The

Fig. 15 (Case 8).—Remote infarction in cerebrum related to embolism. Arteries show moderate sclerosis but without narrowing of the lumens. Eosin-hematoxylin stain; × 9.5.



onset of hemiplegia at the age of 37 tends to rule out an arteriosclerotic etiology; in view of the negative serology for syphilis, cerebral infarction due to syphilitic endarteritis is unlikely. Impaction of an embolus in a branch of the middle cerebral artery, followed by retrograde appositional thrombosis

Fig. 16 (Case 9).—Old myocardial infarction, silent clinically. The involved portion of the ventricle is thinned and fibrotic and lodges an adherent, friable thrombus.

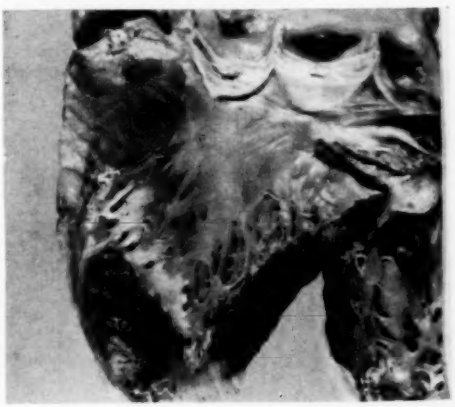


Fig. 17 (Case 9).—Transection through the infarcted myocardium seen in Figure 16. The fibrotic myocardium forms a pouch, which serves as a source of embolic material.

in the obstructed artery, would account for formation of the huge pseudoporencephalic infarct and the corresponding clinical neurologic symptoms and progressive deterioration which occurred in this case. Like Case 2, this case demonstrates the difficulty in diag-

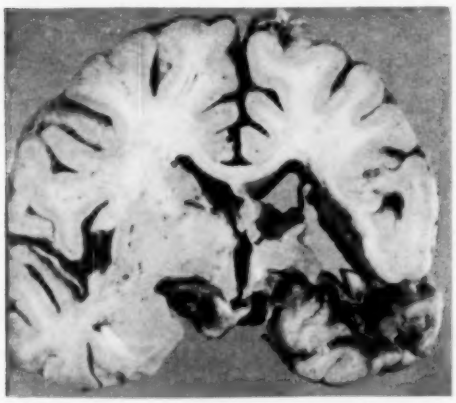


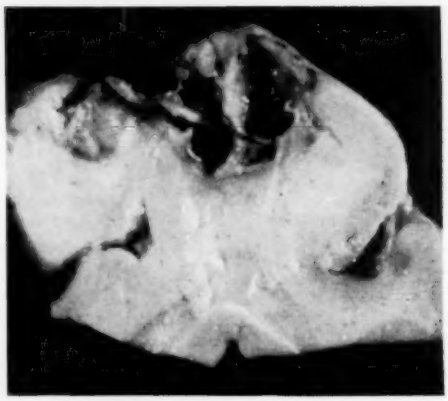
Fig. 18 (Case 9).—Massive embolic pseudoporencephalic defect. Ten-year history of hemiplegia of sudden onset.

nosing cerebral embolism when the cardiac symptoms remain silent or are obscured by severe neurologic symptoms.

Case 10 (Autopsy 10170; man, 48 years).—This patient was known to have had two "heart attacks" between the ages of 40 and 48 years. There was electrocardiographic evidence of myocardial damage. Five weeks before death he suddenly became aphasic; this episode was followed by maniacal behavior; he was admitted with the diagnosis of acute psychosis. Autopsy revealed old and recent myocardial infarcts with a mural thrombus in the left ventricle. In the left frontoparietal area of the brain there was a large subacute infarction.

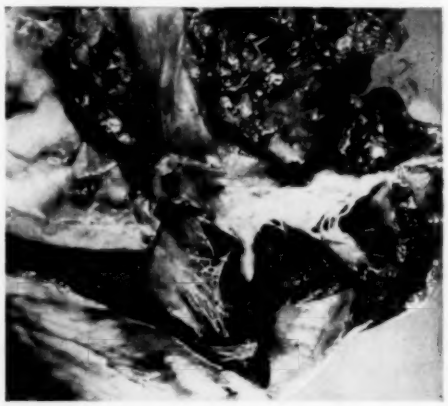
This case, again, illustrates the frequent failure to relate coexistent cardiac and cerebral disease during life. Despite the patient's relatively young age at the time of onset, the

Fig. 19 (Case 11).—One of the multiple focal infarcts which contributed to the clinical symptom pattern of diffuse organic cerebral disease. The lesions involved the cortical gray matter mainly.



known myocardial infarction, and the sudden appearance of the central nervous system symptoms, the diagnosis merely of cerebral arteriosclerosis was applied. At autopsy the cerebral arteries were found to be strikingly free of sclerosis.

Fig. 20 (Case 12).—Old rheumatic heart disease with mitral stenosis and a large left atrium housing a massive adherent, friable thrombus.



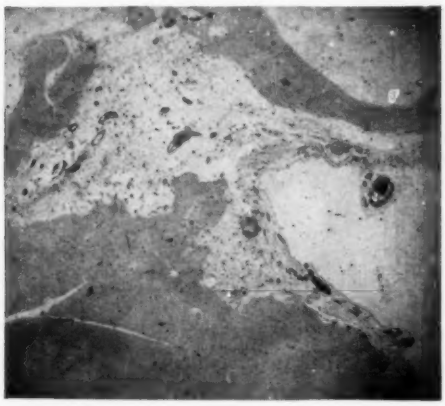


Fig 21 (Case 12).—Area of remote infarction. Despite the age of the patient, there is little arteriosclerosis; lumens contain embolic material. Eosin-hematoxylin stain; × 6.

Case 11 (Autopsy 10665; woman, 76 years).—This patient had a "heart attack" two years before death. Prior to this illness she had been employed and was mentally stable. Progressive dementia developed after the cardiac illness; she became combative, destructive, and hallucinatory. Autopsy disclosed an extensive myocardial infarction and an associated mural thrombus. Embolic lesions were evident in the kidney, intestine, spleen, and brain. The lesions in the brain (Fig. 19) were multiple, ranging from 5 to 20 mm. in diameter, were distributed mainly through the cortical gray matter, and showed old and recent necrosis.

Clinically this patient showed no localizing cerebral symptoms but presented mental changes suggestive of a diffuse process. The finding at autopsy of multiple scattered small embolic lesions supported the clinical impression of a diffuse cerebral process.

Rheumatic heart disease was the cardiac factor in five cases of recurrent cerebral embolism in this study. In each instance there was mitral stenosis with wide left auricular dilatation; these cardiac alterations, in the presence of fibrillation, readily invite the formation of intra-atrial thromboses which may embolize at any time.

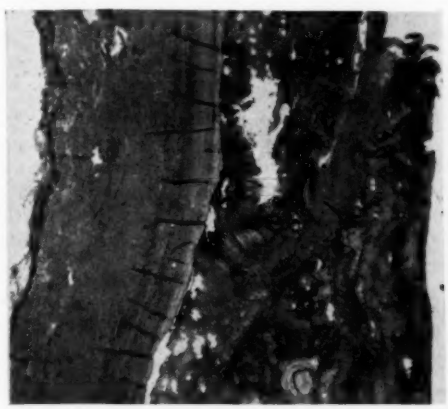
Case 12 (Autopsy 10800; woman, 40 years).—This patient was known to have had old rheumatic heart disease with frequent episodes of decompensation. During adulthood she suffered recurrent epileptic seizures, which increased in frequency. There had been noticeable mental flattening during the last five years of life. Autopsy showed severe mitral stenosis with a huge, partially calcified thrombus in the enlarged left atrium (Fig. 20). Infarcts were present in the kidney and brain. The cerebral arteries were free of sclerosis; in some, emboli were evident microscopically (Fig. 21). In the superior temporal gyrus there was a 1.5 cm. area of infarction.

The infarct in this brain was very old and clearly embolic in genesis. The lesion, so created, represented an epileptogenic focus which was responsible for the seizures present in this patient.

Case 13 (Autopsy 10172; man, 63 years).—Mental changes began 10 years before death, at the age of 53 years. At 58 there was onset of petit mal seizures; the patient became mentally dull. Later, gait disturbance developed. Cardiac fibrillation and murmurs were present during the last three years of life. Central nervous system symptoms were attributed clinically to cerebral arteriosclerosis. Autopsy showed old rheumatic heart disease with stenosis of the mitral and aortic valves; multiple infarcts, up to 4 cm. wide, were present in the frontoparietal areas of the cerebrum. Infarcts were present in the spleen. The arterial system showed little sclerosis.

In the presence of cardiac fibrillation and old rheumatic heart disease with mitral stenosis, it is logical to conclude that the old visceral infarcts in this case were the result of embolism arising from intracardiac thrombi present in the past. Although cardiac disease was clinically evident here, its type and relationship to the cerebral disease were not recognized clinically.

Fig. 22 (Case 16).—Rheumatic heart disease; wall of the left atrium with thickened intima and adherent, but crumbling mural thrombus. Eosin-hematoxylin stain; × 16.



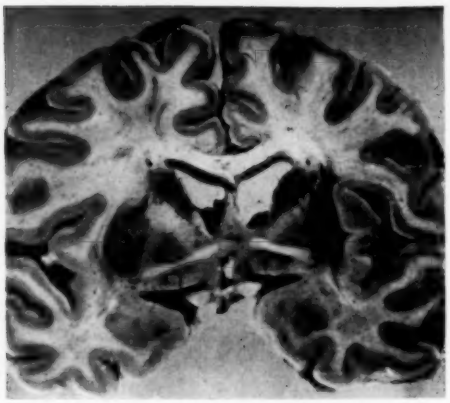


Fig. 23 (Case 16).—Cleft-like infarct in the region of the left putamen and extending into the claustrum. Other smaller, scattered infarcts are evident. The cerebral arteries in this 53-year-old rheumatic patient show little sclerosis.

Case 14 (Autopsy 9619; woman, 73 years).—During the last six months of life this patient showed rapidly progressing mental changes, attributed clinically to cerebral arteriosclerosis and manic-depressive psychosis. Cardiac disease was not evident during life. Autopsy revealed old rheumatic heart disease with mitral stenosis. A well-organized mural thrombus was present in the left ventricle. There were multiple small infarcts in the cerebrum—some recent, some old. There was a terminal infarction of the small intestine.

This case, again, illustrates the difficulty in diagnosing cerebral embolism if the diagnosis of heart disease escapes detection during life. Clinically, the diagnosis of manic-depressive psychosis with cerebral arteriosclerosis had been made. There was no significant arteriosclerosis at autopsy; the pattern of manic-depressive psychosis, latent in this patient, was apparently activated by the embolic lesions in the brain.

Case 15 (Autopsy 10482; woman, 53 years).—This patient had severe rheumatic heart disease at the age of 6 years; cardiac disability with fibrillation persisted through adulthood; mental changes were gradual. Autopsy revealed severe mitral stenosis; the left atrium was enlarged to approximately four times the average size. An infarct 3 by 4 cm. was present in the brain; there was little cerebral arteriosclerosis.

Case 16 (Autopsy 10498; man, 79 years).—This patient presented no history of rheumatic fever or other cardiac disease during early life. Cardiac fibrillation was discovered at the age of 55. In the last three decades of life the patient had shown mental symptoms, with rapid deterioration during the last five years. In the last two years convulsive seizures occurred. Autopsy revealed a rigid mitral stenosis; the greatly enlarged left atrium harbored a mural thrombus 7 cm. wide, which was adherent but friable (Fig. 22). The brain showed three areas of infarction of varying age; the largest infarct was a cleft-like defect, 4 cm. wide, in the area of the left putamen, external capsule, and adjoining claustrum (Fig. 23).

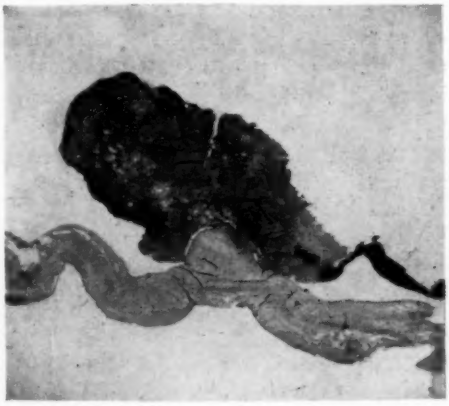
This case portrays a patient with a basic psychotic endowment which in late years was activated by the embolic process. The cardiac disease was not correlated with the central nervous system symptoms; the organic component in the psychotic process was not appreciated clinically.

In the course of the entire autopsy survey there were observed three cases of thrombotic, nonbacterial endocarditis having unusually large valvular thrombi. In one case frank embolization occurred.

Case 17 (Autopsy 10590; woman, 79 years).—This patient had, with age, gradually become physically weakened and bedridden. Twelve months before death a sharp change in behavior occurred. The patient became violent and destructive. At autopsy the brain showed a localized area of softening in the right cerebrum; there was no significant sclerosis of cerebral arteries. In the heart, mitral leaflets bore friable thrombi up to 10 mm. wide, characteristic of vegetations described in cases of nonbacterial thrombotic endocarditis (Fig. 24).†

† References 9 and 11.

Fig. 24 (Case 17).—Thrombotic nonbacterial endocarditis; mitral leaflet saddled by friable, slightly adherent thrombus. Eosin-hematoxylin stain; × 6.



It is known that friable vegetations of nonbacterial endocarditis may become fragmented and embolize to the brain.[11] In this patient the physical deterioration of aging was complicated by the development silently of nonbacterial endocarditis. With embolization of the mitral vegetations, cerebral infarction occurred. The sharp psychotic change of organic nature ultimately manifested by this patient can be related to the impact of the cerebral embolism.

With reference to age, data in this survey indicate that cerebral embolism is commonly a disease of young adulthood and middle age. Onset of symptoms in the third and fourth decades was common. Approximately one-half the patients showed initial cerebral symptoms before the age of 50.

The duration of neuropsychiatric symptoms in the 17 cases of recurrent cerebral embolism recorded here varied from several weeks, in the subacute cases, to 30 years, in the extreme. In general, with recurrent cerebral embolism, the period of neurologic disease extended over a span of 4 to 10 years. The patients in the rheumatic cardiac group tended to have a more prolonged course.

The gross pathologic lesions found in the brain at autopsy varied. In most cases there was a principal area of necrosis in the cerebrum and other, scattered smaller lesions. The commonest sites of involvement were the motor cortex and the area of the corpus striatum with adjoining internal capsule. Such lesions were present in eight cases, and there was, clinically, associated hemiplegia in these patients. In some instances the lesions were small and scattered; mental deterioration dominated the clinical course in these cases.

The incidence of recurrent cerebral embolism in patients with old myocardial infarction was evaluated in the present study. In this series, of 538 consecutive autopsies, there were 54 cases with old myocardial infarction of gross proportions; 14 harbored mural thrombi in the left side of the heart. In 10 of these cases the persisting intracardiac thrombi were the source of recurrent embolization to the brain.

In the entire autopsy series there were 34 cases of old rheumatic heart disease having a significant degree of chronic mitral or aortic valve involvement. Of this rheumatic group, five, or approximately one in seven, showed distinct evidence of cerebral embolism.

COMMENT

There has long been evident in neuropathology a need for closer correlation between diseases of the brain and other organic diseases of the body. Too often, lesions present in the brain and lesions present in other organs, though in fact related, have been divorced in clinical practice and in the pathology laboratory. It is in this way that the problem of chronic cerebral disease due to recurrent embolism has in large measure escaped notice.

It is evident that the diagnosis of recurrent cerebral embolism is manifestly difficult; in the present series of cases the diagnosis was made clinically only once. Increased interest in this problem is warranted since it may be that cerebral embolism, diagnosed, may lend itself to anticoagulant therapy and its recurrence stayed.[18]

The brain is the most vulnerable and the most feared site of embolization in the systemic arterial circulation. The effect of cerebral embolization depends on the site and the extent of the resulting cerebral infarction. If the embolic insult is massive or involves a vital regulatory center in the brain, there is precipitate death. However, the present study tends to dispel the textbook inference that cerebral embolism is generally a fatal process. As is evident in this investigation, embolic cerebral lesions often are sublethal; the victim is left with a crippled cerebral function and the prospects of recurrent embolic visitations.

Cerebral embolism cannot be diagnosed clinically if the cardiac disease is unannounced. As was evident in Cases 2 and 14, the heart may, altogether silently, bear the burden of myocardial infarction or mitral stenosis and harbor mural thrombi; the cardiac disease, developing asymptomatically, escapes detection during life. Mitral stenosis, for ex-

ample, is frequently observed in the autopsy room in cases which during life presented no cardiac symptoms. Boyd and Werblow [19] point out that approximately one-third of cases with proved coronary thrombosis manifest no pain during life. In such patients with obscure cardiac status the diagnosis of cerebral embolism clinically remains an enigma.

The presenting symptoms in a patient with cerebral embolism may be overwhelmingly neurologic; the cardiac genesis of the syndrome may be completely masked clinically by the preponderance of central nervous system symptoms. Dozzi [20] in a study of 1,000 consecutive autopsies, found 12 cases having both coronary thrombosis and cerebral lesions; in 10 of the cases, because of the overwhelming central nervous system symptoms, the cardiac lesion had escaped notice during life. Likewise, in patients with chronic valvular disease, clinically silent, the first indication of illness in the patient may be focal cerebral symptoms; Friedberg [6] noted that cerebral embolism may be the first clue to the presence of mitral stenosis.

Patients with sudden hemiplegia, diagnosed clinically as apoplectic hemorrhage, again and again prove at autopsy to have cerebral embolism. In adults exhibiting chronic progressive mental and neurologic deterioration, even though they be middle-aged, the disease is often categorically labeled cerebral arteriosclerosis; the embolic genesis of the cerebral deterioration, finally revealed at autopsy, comes as a surprise to the clinician. Of the 17 cases of recurrent cerebral embolism in the present study, only 1 was so diagnosed before autopsy. In the differential diagnosis of chronic neuropsychiatric disorders a consideration of cerebral embolism is usually omitted. The relationship of chronic organic brain disease and chronic cardiac disease is deviative and is often unsuspected during life. In some cases, as observed in the present study, the embolic injury to the brain tended to bring to the surface a latent schizophrenia or other psychosis; the organic component of the cerebral process is overlooked during life. In cases of cerebral embolism, if autopsy is not performed, the true nature of the cerebral disease is buried with the remains and lost forever.

The syndrome of recurrent cerebral embolism tends to make its initial appearance at a relatively early period in adult life. The factor of age may be of assistance clinically in ruling out cerebral arteriosclerosis as the etiologic process and in considering embolism in these cases. Dozzi [20] points out that cerebral embolism is particularly prone to occur in adults of the younger age group after myocardial infarction. Mitral stenosis, which is commonly an antecedent in cerebral embolism, is a cardiac complication of young adults. As noted in Table 2, cerebral symptoms related to embolism appeared during young adulthood of middle age in approximately half the cases in this study. Accordingly, young adults, particularly those with a past history of cardiac disease, who present sudden onset of neurologic symptoms should be suspected of embolic cerebral disease. It is generally realized that the incidence of coronary occlusion in the younger age group is increasing; accordingly, an increased frequency of cerebral embolic disease may be anticipated in this segment of the population.

In this group of patients with chronic cerebral disease due to embolism, the recurrent nature of the process was evident both in the clinical course and in the anatomic findings at autopsy. In most instances gradual neurologic deterioration was punctuated by staccato episodes of hemiplegia, aphasia, or other circumscribed symptoms; these acute clinical attacks corresponded to the cyclic showers of emboli being distributed to the brain and other viscera. In most instances the recurrent nature of this process could be correlated clinically and morphologically; echoing the clinical background, infarcts in the brain, some ancient, some of intermediate age, and some recent, were present at autopsy. In some cases, a chronic neuropsychiatric course was initiated by a single recorded ictus; and at autopsy only a single large infarct, usually ancient, was

apparent. Mural thrombi, in each case, were present in the heart. Six such cases of chronic cerebral embolic disease initiated by a single ictus were included in this series, albeit they were not overtly recurrent. Embolic disease, whether occurring in the brain, lung, or other sites, if not immediately fatal, tends by its inherent nature to be of multiple issue and recurrent. Clinically, minor embolic episodes may elude notice during life. Morphologically, small infarcts may become grossly imperceptible in the process of time. Hence, cases at autopsy with single gross infarction of the brain and persisting thrombi in the heart were included in this series.

Cerebral embolism develops unpredictably in patients who have myocardial infarction and may supervene insidiously after a delay of many years. Likewise, in patients with old mitral stenosis, with hearts in fibrillation, the onset of cerebral embolism is a constant threat. In the present survey of autopsies, approximately one-fifth of the cases with old myocardial infarction, one-seventh of cases with mitral stenosis, showed evidence at autopsy of recurrent cerebral embolism; this indicates the high potential susceptibility of this group of cardiac patients; however, because of the selected nature of the institutional population in the present study, the relative incidence of cerebral embolism noted here may not represent the actual cross-sectional incidence of cerebral embolism in cardiac patients in general. It is pertinent to realize that the presence or absence of intracardiac thromboses cannot be directly ascertained during life. All patients who survive the immediate effect of myocardial infarction, and all patients with mitral stenosis, are, in fact, for all their remaining days, vulnerable to an embolic assault on the brain.

Patients with recurrent cerebral embolism, though the most obvious symptoms may be neurologic or psychiatric, invariably have a serious underlying heart disease. The bivalent character of this syndrome is usually given little consideration. If the cardiac symptoms appear early, the patient, referred to the cardiac clinic, may lastingly be treated for his heart symptoms. If neuropsychiatric symptoms are dominant, the patient will likely be admitted and treated for his nervous system disease. Such treatment of the cardiac aspect, or of the neurologic component, one to the exclusion of the other, is obviously futile. In each case the true nature of the cardiocerebral complex must be recognized and treatment pursued accordingly.

It is evident from this study that recurrent cerebral embolism is of wider occurrence than is generally realized; accordingly, it merits searching attention, particularly in neuropsychiatric practice.

SUMMARY AND CONCLUSIONS

Seventeen cases of chronic organic brain disease due to recurrent cerebral embolism occurred in 525 consecutive autopsies. This study was performed in a neuropsychiatric institution over a period of four and one-half years; in 58% of deaths autopsy was performed.

The diagnosis of recurrent cerebral embolism was generally characterized by a history of chronic cardiac disease; onset of cerebral symptoms commonly occurred in the fourth decade of life; sudden hemiplegia or other episodic neuropsychiatric symptoms intermittently punctuated the steadily deteriorating clinical course. At autopsy distinct cardiac and cerebral defects were demonstrable in each case. The heart in most instances showed an old myocardial infarction, with persisting mural thrombus in the left ventricle or old rheumatic heart disease with mitral stenosis and left atrial thrombosis. Emboli arising from these thrombotic sources produced infarcts in the brain of varying ages and sizes. There were 11 cases associated with myocardial infarction, 5 with old rheumatic heart disease, and 1 with nonbacterial thrombotic endocarditis.

Data derived from this series of autopsies emphasize the vulnerability of cardiac patients to cerebral embolism. Over one-sixth of patients with old myocardial infarction and one-seventh with chronic rheumatic valvular disease suffered recurrent cerebral embolism.

Considering that 4% of the cases of organic brain disease in this series were associated with recurrent cerebral embolism, this syndrome warrants increased clinical attention in neuropsychiatric practice. As awareness of this syndrome matures, diagnostic accuracy will increase. Recent advances in the treatment of thromboembolic disease have initiated means of interrupting the chain of phenomena leading to recurrent cerebral embolism. With further progress, adequate prophylaxis may become available, and with it the prospect that in patients vulnerable to embolic disease of the brain the onset may be averted, and in patients stricken its recurrence may be prevented.

Mrs. Margaret Hamilton assisted in the organization and preparation of this manuscript, and Mr. Gilford Millard aided in preparing the photographs.

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HYPOPHYSICTENY WITH RADIOACTIVE CHROMIC PHOSPHATE IN TREATMENT OF CANCER

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THE FIRST recorded instance of operative removal of the human hypophysis was reported by Chabanier, Puech, Lobo-Onell, and Lélu in 1936.[1] The operation was performed on a patient suffering from severe diabetes. A transfrontal approach was employed and the gland was removed by dissection, suction, and coagulation anterior to the optic chiasm. The patient survived, and the diabetes became more manageable. About the same time Elden[2] reported a case operated upon by Van Wagenen, in which the anterior lobe of the hypophysis had been largely destroyed by coagulation. The patient developed all the clinical manifestations of a severe pituitary deficiency. At autopsy, seven years later, remnants of glandular tissue were found.[3]

Hypophysectomies for malignant lesions were reported in 1952 by Perrault, Le Beau, Klotz, Sicard, and Clavel[4] and by Shimkin, Boldrey, Kelly, Bierman, Ortega, and Naffziger.[5] In both instances the progress of the malignant disease appeared to be retarded.

The first actual series of cases of destruction or removal of the hypophysis, 26 in all, was reported by Luft and Olivecrona in 1953.[6] The series included 3 cases of Cushing's syndrome, 7 of malignant hypertension, 4 of diabetes mellitus, and 12 of malignant tumors of various types. This article is at present the definitive publication and deserves special study.

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Of the patients with Cushing's disease, one was apparently well (after coagulation of the hypophysis in two stages), one died a few days after a similar operation of suffocation from an undiagnosed bronchial carcinoma, and the third died on the third postoperative day (after an operative removal) of a sudden unexplained drop of blood pressure. The authors recommend leaving some of the gland intact in this condition.

In all other cases in the series, the gland was removed by dissection.

Of the patients with diabetes, one was substantially improved; the other three died of cerebral complications of obscure nature.

Two patients with malignant hypertension survived the operation two and five months respectively, and then died of uremia. The other five all died within a few days of operation, two of intracranial hemorrhage and three of edema of the brain.

There were no surgical deaths among the 12 cases of malignant tumors. Marked but temporary improvement occurred in the following cases: one each of carcinoma of the prostate and hypernephroma. In a case of malignant chorioepithelioma, the patient died of unrelated causes eight months after hypophysectomy, and no traces of the tumor were found at autopsy. One patient with extremely advanced, ulcerating carcinoma of the breast was well and doing her housework eight months later, the ulcerations having healed. In three cases, also of carcinoma of the breast in which the extirpation was probably incomplete, no improvement was observed. Insufficient time had elapsed to permit a judgment of the results in the mammary carcinomas in the remaining five patients.

In a case reported by Knowlton, Pool, and Jailer,[7] complete removal of the hypophysis in a patient suffering from Cushing's syn-

drome and a metastatic adrenocortical carcinoma did not appear to retard the growth of the metastases. The patient came to autopsy seven weeks after operation.

Hypophysectomy has also been employed, with beneficial results, in two out of four cases of carcinoma of the breast by Pearson, Ray, Harrold, West, Maclean, and Li,* but no complete report has been published. Apparently the operative mortality was high.

In summarizing the results of surgery of the hypophysis, it appears that dramatic improvement has been obtained in cases of Cushing's syndrome, severe diabetes, and certain types of malignant lesions. Particularly in the latter category some of the failures may be attributable to incomplete removal of glandular tissue. The chief drawback to the procedure appears to be the high incidences of postoperative accidents, in particular acute edema of the brain. This occurred in one of Olivecrona's patients, although the operation was limited to transection of the stalk without removal of the gland. Dissection or electrocoagulation of the gland may fail to remove all the functioning cells, as is clear from Luft and Olivecrona's article; in six cases in which the contents of the sella were carefully examined at autopsy, remnants of the gland were found in three. An indication of the formidable surgical problems encountered is also seen in the fact that the operation had to be performed in two stages in two of the cases reported.

It appeared to us, therefore, that a surgical procedure which would completely destroy the gland with a minimum of dissection or manipulation might prove of value.

ORIGIN AND THEORY OF THE PRESENT OPERATIVE PROCEDURE

We have used colloidal radioactive chromic phosphate experimentally in animals in order to study its ability to destroy tissue when injected into various organs. It has been found that when 1 mc. of the material in 1 cc. of solution is injected directly into the brain of dogs, it remains locally, producing an area of necrosis about 0.5 cm. in diameter, and does not enter the blood stream to any appreciable degree. Therefore, there is little danger of radiation effect on the bone marrow. The intensity of the local necrosis presumably corresponds to the energy of the radioactive material, but since only beta radiation is emitted the area of necrosis at the injection site should not exceed the area infiltrated by the fluid by more than 2.5 mm., practically irrespective of the dosage. On the basis of this experimental work, radioactive colloidal chromic phosphate has been used for the local destruction of inoperable prostatic cancer. The preliminary results of this work were recently reported by Rusche and Jaffe.[8] Chromic phosphate has a number of advantages over radioactive colloidal gold, since it has no gamma rays which might be dangerous to those handling it and its physical half-life, of about two weeks, is long enough for convenience in planning a surgical procedure. The relatively short half-life of radioactive gold (3.7 days) makes it necessary to order it immediately before each operation.

A report by Rasmussen, Harper, and Kennedy[9] on the effect of radioactive pellets of yttrium laid upon the exposed surface of the hypophysis of the monkey demonstrates another method of destroying the pituitary gland by the interstitial use of a radiation source. The radioactive pellets of yttrium were deposited on the diaphragma sellae through a transfrontal approach. All animals made a good recovery. Those receiving less than 1 mc. of radiation survived for weeks until killed, while most of those receiving larger doses died within the first three postoperative days. The remainder showed evidence of profound damage to the brain. Histologic studies showed that all cells within 2 to 4 mm. of the pellets were destroyed. The chiasm and other surrounding

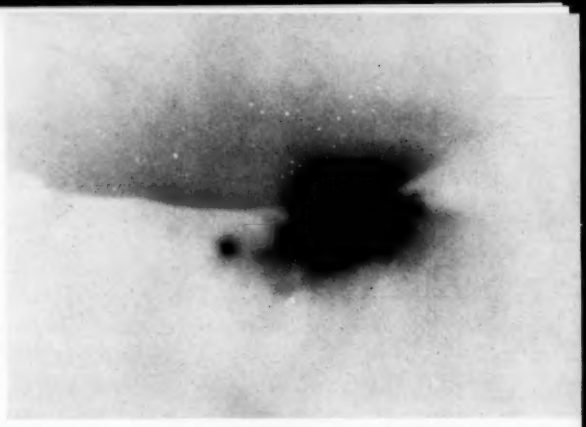
* Pearson, O. H.; Ray, B.; Harrold, C. C.; West, C. D.; Maclean, J. P., and Li, M. D.: Effect of Hypophysectomy on Neoplastic Disease in Man, 36th Annual Meeting of the Endocrine Society, San Francisco, June 17-19, 1954.

tissues were destroyed about equally with the hypophysis, but the destruction of the glandular cells was never complete.

As compared with radioactive yttrium in pellets, the liquid colloidal chromic phosphate has the advantage that it diffuses through the hypophysis when injected with a fine needle. These advantages would appear to be at their maximum in an area such as the contents of the sella, in which a circumscribed gland of loose mechanical structure is almost completely surrounded by a dense capsule. As compared with desiccation or electrocoagulation, the gradual destruction of secreting tissue would seem to be an advantage. There is little danger of postoperative hemorrhage, and there has not been any noticeable edema of the brain, since this radiation material acts at an average distance of 2.5 mm. from the injection site. If one distributes the material fairly evenly within the pituitary gland, there should be no danger of necrosis of the sella or of the surrounding brain tissue.

The radiation dose chosen was 10 mc. of chromic phosphate in a volume of 2 cc. From our own observations and from the work of Rasmussen and co-workers, this would appear to be 5 or 10 times that of the minimum necrotizing dose. A drop of sterile 1% methylene blue solution is added to the radioactive material to facilitate identification of the dispersion of the solution. In practice, a Geiger counter seldom identifiies any radioactivity not already marked by the blue dye.

In one of our patients who died on the second postoperative day as a result of a pulmonary accident, the autopsy material showed an excellent concentration of the radioactive colloidal material in the pituitary gland, as the radioautograph illustrates (Figure). It is estimated that the pituitary receives between 2,000,000 and 5,000,000 beta roentgen equivalents physical (rep) in this procedure.



Radioautograph of sagittal section of sella and contents (Case 4), showing distribution of radioactivity two days after injection.

SURGICAL TECHNIQUE

The actual surgical procedure is simple. A standard right frontal flap is turned down, and the dura is opened along the sphenoid ridge. The frontal lobe is gently retracted, revealing the right optic nerve and chiasm. Between the chiasm and the anterior clinoids, a grayish web of arachnoid is seen. This is gently brushed away with pledgets, finally revealing the diaphragma sellae. Anteriorly, the orange-colored anterior lobe may be seen through it; on either side are the carotid arteries, and the stalk is posterior.

When all bleeding is controlled and the site of injection is visible, a 1 cc. tuberculin syringe of the radiation solution carrying a 5-cm. long 25-gauge needle is handed to the operator by the radiotherapist. If a drop of fluid exudes from the needle, it is carefully wiped away. The needle is then inserted just posterior to the anterior clinoids and advanced gently until the base of the sella is palpated. The contents of the syringe are then injected slowly over a period of about two minutes. The glandular tissue can be seen to grow diffusely blue. If any trace of blue-tinged fluid escapes, it is sponged away, the needle is withdrawn, and a fresh puncture is made. Usually two syringefuls are injected through three or four puncture sites. All of the pledgets in the wound are collected in a special basin, and the wound is thoroughly washed with large quantities of isotonic solution.

The wound is closed in the usual fashion. A careful survey of the gloves, gowns, drapes, and instruments is made with the portable Geiger counter. So far, no noteworthy radiation contamination has been found.

This operation is obviously not a hypophysectomy. To avoid the clumsy phrase "destruction of the hypophysis by injection of radioactive material," we propose the term "isotope hypophysicteny."

SELECTION OF CASES, PREOPERATIVE AND POSTOPERATIVE STUDIES, SURGICAL RESULTS

All of our cases have been patients in apparently terminal stages of malignant tumors: three of carcinoma of the breast,

two of carcinoma of the thyroid, one of carcinoma of the prostate. As will be seen from the case histories, there were evidences of metastases in all. All were in pain and were receiving narcotics.

Judgment of the completeness of destruction of the hypophysis by any means is difficult. We have attempted to evaluate the adequacy of this operative procedure by use of as many different indicators as seems feasible. The tests we have employed may be listed as follows:

A. Tests of anterior pituitary function per se
   1. Twenty-four-hour urine gonadotropin (F. S. H.) excretion
   2. Four-hour epinephrine eosinophile test
   3. Insulin tolerance test
B. Tests of functional activity of anterior pituitary target (gland)
   1. Thyroid
      (*a*) Serum protein-bound iodine (P. B. I.)
      (*b*) Thyroid radioactive iodine uptake
   2. Adrenal cortex
      (*a*) Twenty-four-hour urinary 17-ketosteroid excretion
      (*b*) Twenty-four-hour urinary 11-oxysteroid excretion
      (*c*) Serum electrolytes
         1. Serum sodium
         2. Serum potassium
         3. Serum chloride
         4. Serum CO_2
   3. Gonads
      (*a*) Twenty-four-hour urinary excretion of 17-ketosteroids
      (*b*) Twenty-four-hour urinary excretion of estrogens

A later report will deal with the alterations in these values produced by the operation. This communication is intended to cover the surgical technique and immediate results.

Ordinarily no special preoperative medication is given.

In order to prevent the development of postoperative adrenocortical insufficiency, we have routinely instituted the administration of cortisone immediately after the completion of the surgical procedure. A total of 300 to 400 mg. of cortisone is given intramuscularly in divided doses during the first 24 hours postoperatively. Thereafter, the daily dose is progressively decreased until the final maintenance dose of 25 mg. orally is reached, between the 10th and the 14th postoperative day. Supplemental sodium chloride, 1 to 4 gm. daily by mouth, is begun on the second to the fourth postoperative day, and the dose is determined by the amount of salt necessary to maintain normal serum electrolyte levels. Our preliminary experience would indicate that these patients tend to develop low serum sodium and serum chloride concentrations unless supplemental sodium chloride is administered. The patients are discharged from the hospital two to three weeks postoperatively on a regimen of oral cortisone, 25 mg. daily, and sodium chloride, 1 to 4 gm. daily. No other replacement therapy has been given thus far, but at the time of the writing of this preliminary report it seems probable that patients also need thyroid extract and androgens to prevent the development of postoperative anemia and leucopenia.

There have been no obvious surgical accidents so far. One patient died, apparently of acute pulmonary edema, on the second postoperative day. Autopsy showed that the operative site was in perfect condition. Examination of the contents of the sella will be reported in detail in another communication.

The other five patients made an excellent surgical recovery. Pain was relieved or reduced in all cases. One patient (cancer of the breast) is carrying on her daily activities without any pain medication three months after surgery. One patient (thyroid cancer) developed diabetes insipidus in the third postoperative week, which was still present two months after surgery. Another (thyroid cancer) developed evidences of a severe depression of the bone marrow one month after the operation; now, three weeks later, the condition is completely back to normal, after several blood transfusions and institution of complete endocrine replacement therapy. There has been a tendency to moderate normochromic anemia and leucopenia in the

other cases also. Our preliminary impression is that these hematologic abnormalities are due to incomplete endocrine replacement therapy, and that the hematologic picture is being restored to normal with the institution of complete replacement therapy (thyroid extract and androgens in addition to cortisone). So far, there is no objective evidence of radiation depression of the bone marrow.

REPORT OF CASES

CASE 1.—N. S., a married woman of 47, was first seen in the Cedars of Lebanon outpatient department on June 11, 1952, complaining of swelling of the right arm. She gave the history of having had a radical right mastectomy at the Middlesex Hospital in London in October, 1951, and showed a well-healed scar. A course of postoperative irradiation had been given. The swelling of the arm was considered to be a postoperative lymphedema, but no evidences of metastasis were found at that time.

In April, 1953, she complained of pain in the spine. X-rays showed evidence of a spinal metastasis. The pain grew gradually worse, and in June she was given a course of pelvic radiation to produce a castration.

Over the following year her pain reappeared, and it became clear that the metastases were growing once more. She had widespread osteoblastic and osteolytic metasteses to the pelvis, hips, and lumbar spine. The situation was clear to the patient and she accepted an operation on the hypophysis, when the possibilities were explained to her. An isotope hypophysicteny was carried out after a preliminary endocrine survey, on June 25, 1954. She made an excellent operative recovery and was discharged from the hospital free of pain and in excellent general condition. When last seen, on Oct. 1, she was still in good condition, doing her housework and free of pain. She had developed a moderate normochromic anemia and leucopenia despite iron therapy during the entire postoperative period.

CASE 2.—R. L., a 39-year-old married woman, had an excision of a thyroid nodule in 1951. Microscopic diagnosis was papillary adenocarcinoma Grade 3 invading the capsule and extending into the anterior wall of the trachea. Not all of the tumor could be removed at surgery and for this reason she was given immediate postoperative deep x-ray therapy.

Shortly after the original surgery there was prompt recurrence. A modified right radical neck dissection was performed and radon seeds were implanted. Additional x-ray therapy was also given.

The patient was first seen in the Department of Radiation Therapy on Sept. 9, 1952, at which time her thyroid gland radioiodine uptake was 30%. She has been given repeated doses of radioiodine, but no evidence of significant uptake in the metastatic lesions was ever noted. Numerous large metastases developed in both lungs. Repeated bone surveys were negative until June 30, 1954, at which time a suggestion of a small metastatic tumor in one of the parietal bones was noted. At this time radioiodine tracer studies revealed no uptake in the thyroid region in the neck or in the metastatic lesions. No radioiodine uptake could be induced in the metastatic tumors despite the administration of large doses of thyroid-stimulating hormone (T. S. H.) over a period of 10 days.

Because of the progression of the disease and the failure to induce the tumors to pick up radioiodine, an isotope hypophysicteny was performed on July 14. The operation was well borne, and the patient's condition never gave cause for anxiety. The pain and severe cough were almost immediately relieved and she required no further narcotics.

After steady improvement, she was discharged from the hospital on July 27. The patient developed diabetes insipidus in the third postoperative week and this is still present, two months after surgery. The polyuria is controlled by injections of vasopressin (Pitressin) tannate in oil two times weekly. This patient also developed a moderate normochromic anemia and leucopenia in the second postoperative month. She is now capable of light housekeeping activities.

CASE 3.—L. P., an optometrist of 51, was operated on in February, 1952, for a carcinoma of the thyroid gland. A total right lobectomy and a right radical neck dissection were performed.

He had been treated with postoperative x-ray therapy. Serial x-rays revealed metastatic lesions in both lungs, which progressed. Because of the progressive nature of the disease and the inability to make the lesions take up radioiodine, despite the administration of large doses of thyroid-stimulating hormone (T. S. H.) for 10 days, an isotope hypophysicteny was performed on July 20, 1954.

Recovery was uneventful and he became free from pain, although somewhat weak. On Aug. 18 he developed gross hematuria and ecchymoses, which were found to be due to severe bone marrow depression (anemia, leucopenia, and thrombocytopenia). This responded to multiple blood transfusions, large doses of cortisone, thyroid extract, and androgens, and three weeks later he had a normal blood count and bone marrow with no bleeding tendencies. When last seen, on Sept. 13, he was well and had a normal blood count. The response to endocrine therapy suggests that this bone marrow depression was not due to radiation effect. Bone marrow and blood studies did not show any signs of radiation activity.

CASE 4.—B. S., a married woman of 53, was first seen in the outpatient department of the Cedars of

Lebanon Hospital in March, 1945, complaining of pain in the right side of the neck and enlargement of the thyroid gland. She gave the history of having had a bilateral radical mastectomy the year before, with postoperative x-ray therapy. No evidences of metastasis were seen, but she had an adenoma of the thyroid, which was removed in August, 1947.

In April, 1949, she noticed a painless nodule in the left chest wall. Biopsy material was found to be a recurrent carcinoma. The left chest wall lesion was excised in June, but in May, 1951, she began to complain of severe pain in the left shoulder. Gradually masses developed about the scapula and biopsy tissue showed a recurrence of neoplasm. She was given additional x-ray therapy. In October, 1953, she developed a pleural effusion. The fluid contained malignant cells. Radioactive colloidal chromic phosphate was injected intrapleurally on five occasions, but she began to go downhill rapidly, with metastases to the lungs and several bones.

Destruction of the hypophysis was suggested and accepted by the patient. After a preliminary endocrine survey, 10 mc. of radioactive chromic phosphate was injected into the hypophysis on Aug. 6, 1954. She made an excellent surgical recovery and was discharged on Aug. 29, in good condition and free of pain. She was still doing well, being up and about, and comfortable when last seen on Oct. 2. There had been no recurrence of the pleural effusion.

Case 5.—P. N., a 47-year-old white man, was first admitted to the Cedars of Lebanon Hospital on Dec. 15, 1953, complaining of pain in the cervical spine region radiating toward both shoulders, of three months' duration, not helped by diathermy treatment. A general medical survey failed to reveal a cause for it. Rectal examination revealed enlargement of the prostate, chiefly involving the right upper lobe, which was stony hard, and a biopsy on Dec. 23 showed adenocarcinoma of the prostate. The case was followed carefully and symptomatic palliative treatment consisted of estrogen, deep x-ray therapy, and cortisone.

X-ray examination of March 15, 1954, showed osteolytic metastasis to the right iliac bone, in addition to the fourth cervical vertebra. X-ray examination of May 22 showed a large, soft-tissue tumor mass in the pelvis, in addition to the osteolytic lesions described above. Chest x-rays were negative. Gastrointestinal series showed a soft-tissue mass in the anterior portion of the pelvis, causing extrinsic pressure deformity of the sigmoid and displacement posteriorly.

The patient received deep x-ray therapy to the areas of metastases with good palliative results, in addition to estrogen and cortisone therapy. An orchiectomy was refused. His course was progressively downward with a marked anemia developing in July, which was interpreted as being caused by extensive bone marrow involvement by disease. Many supportive transfusions were given, with only temporary benefit.

The patient was obviously close to death when the procedure of hypophysicteny was discussed, and this was performed on Sept. 1, with a total of 10 mc. of radioactive colloidal chromic phosphate injected. The patient was in poor condition at the time of operation. The evening of the operation he lapsed into a severe adrenal deficit, from which he recovered. He was doing apparently well, conscious, eating and drinking until the morning of the second postoperative day, when he suddenly complained of pain in the left chest and cough, became very dyspneic, and died in a few minutes.

Autopsy showed the carcinoma of the prostate, with widespread metastases. The operative site was in good condition, without evidence of cerebral edema or subdural hematoma. There was, however, a small left pleural effusion and pulmonary edema, which appeared to be the immediate cause of death. A radioautograph of the content of the sella is shown in the accompanying Figure.

Case 6.—Mrs. D. A., a 36-year-old white woman, was referred on Sept. 13, 1954, with a history of having a right breast tumor excised in June, 1953. Because biopsy of a specimen from the right supraclavicular nodes showed metastatic carcinoma and because the patient had extensive fixed lymph node metastases in the right supraclavicular region as well as in the left cervical area, the case was considered too far advanced for a radical mastectomy. A bilateral oophorectomy was performed and this was followed by deep x-ray therapy to the right breast area, right axilla, and supraclavicular metastatic nodes and to the metastases in both sides of the neck. This resulted in some regression of the extensive disease.

Testosterone was given by injection three times a week for five weeks beginning June 15, 1954. When the patient showed progression of disease, which now involved both breasts as well as the anterior chest wall, in addition to the previously described areas, she was given 100 mg. of cortisone daily. This was continued until two weeks prior to admission. This resulted in some temporary subjective improvement. On admission the patient complained of a feeling of tightness in both sides of the neck, making breathing somewhat difficult. There was pain and swelling in the region of the left parotid gland and the left ear, and Bell's palsy on the left of two weeks' duration. The patient had required about five doses of narcotics a day to control her pain. She also had hot flushes since the oophorectomy. She had had no children, and there was no family history of breast cancer.

On examination there was limitation of motion of the left eye, and an inability to close completely the left upper lid. Both sides of the neck and the

left parotid area were occupied by fixed, stony-hard metastatic cervical lymph nodes, and the pulse and blood pressure could not be obtained on the right side. On the left side the blood pressure was 130/90; pulse 120, good quality. The left breast showed evidence of metastatic cancer, and the liver was enlarged, hard, and nodular. The skin over the entire anterior chest wall, especially on the right, had numerous areas of metastatic involvement. There was residual fixed cancer in the right breast. X-rays of the chest showed enlarged mediastinal nodes in the right hilar region, an elevation of the right diaphragm due to metastatic disease compressing the phrenic nerve, and/or metastatic disease of the liver, and a small amount of fluid in the right pleural cavity. X-ray examination of the bony skeleton showed no evidence of metastases in the pelvic bones, lumbar spine, ribs, or skull. Electroencephalogram was normal.

In view of the fact that the patient continued to develop recurrent neoplastic disease in spite of the prophylactic bilateral oophorectomy performed one year previously, we decided to proceed with the isotope hypophysicteny instead of considering a bilateral adrenalectomy. After preliminary endocrine studies were completed, the isotope hypophysicteny was carried out on Sept. 19. A total of 7.5 mc. of colloidal chromic phosphate was injected into the pituitary gland in 1.5 cc. volume of medium. The patient made an uneventful recovery and left the hospital in 10 days. There were no immediate postoperative complications and there was some noticeable relief of pain. Some immediate regression of the mediastinal and cervical tumor masses was noted. Examination on Oct. 5 showed a normal pulse at both wrists and the blood pressure could be obtained again on both sides.

The patient's doctor reports that she died suddenly, apparently of suffocation from enlarged cervical glands, in November, 1954.

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NEURITIS OF DEEP PALMAR BRANCH OF ULNAR NERVE

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THE PROBLEM of etiologic diagnosis of lesions of the ulnar nerve is commonly encountered by both general practitioners and specialists in disorders of the nervous system. Many causes of ulnar neuritis are well known and easily identified. Trauma along the course of the nerve, metabolic or toxic neuropathies, or compression of the cervical roots usually presents no problem in diagnosis. Degenerative disease of the motor nerves or muscles is usually evident and, in contrast to other causes, sensory changes are usually absent. Frequently, however, the etiology of the ulnar nerve dysfunction remains obscure despite careful history, examination, and x-rays. Therefore, two cases of ulnar nerve dysfunction caused by a rather unusual mechanism will be described. Their interest lies not only in the peculiar etiology but also in the complete absence of associated sensory loss, the only finding being that of atrophy and weakness of the muscles supplied by the ulnar nerve.

The clinical findings suggest that these cases fall into the group analyzed by Hunt,[1] in 1908, as "Occupational Neuritis of the Deep Palmar Branch of the Ulnar Nerve" and first described by Gessler [2] in 1896.

REPORT OF CASES

CASE 1.—R. B., a 43-year-old housewife, first noted decreased strength in her right hand in April, 1953. In addition to weakness, she complained that the hand was extremely awkward. There were no associated sensory complaints. Two months after the onset of symptoms she noted wasting of the muscles on the dorsal surface of her right hand. After ironing or using the hand to excess, the hand would ache but there were no complaints of numbness or tingling. Past history supplied no additional significant information with reference to the present illness. The patient had never injured the arm or neck and had no other symptoms suggesting more extensive neurologic or general systemic disease. The patient has a child with severe cerebral palsy who presented a very difficult feeding problem because of involuntary movement and tightness of the jaw musculature. The patient had to spend a great deal of time feeding this child and was in the habit of holding a spoon tightly clenched between the index and middle finger, with the head of the spoon braced tightly against the hypothenar eminence. This pressure was therefore exerted over the area of the deep palmar branch of the ulnar nerve.

Examination disclosed interosseous atrophy evident in the right hand. The hypothenar musculature was soft and flabby but showed no pronounced atrophy. There was weakness of the adductor pollicis and interossei on the right. The grip on the right was slightly weaker than that on the left. The hypothenar muscles on the right were only slightly weaker than those on the left. All other muscle groups of the upper extremity and of the entire body were normally strong. There were no sensory changes. The remainder of the neurologic examination was entirely normal.

Roentgenograms of the cervical spine showed minimal narrowing of the fifth and sixth cervical interspace but were otherwise normal. Roentgenograms of the elbows were normal.

The patient has been carefully followed and examined for over a year. Initially she was advised to avoid all heavy pressure on the palm. During the following year she noted slow but definite return of strength in the weak muscles. Reexamination after one year verified this improvement and also disclosed filling out of the atrophied muscles to nearly normal.

CASE 2.—R. M., a 53-year-old railroad station agent, first noted wasting of muscles of the left hand in August, 1952. Mild associated weakness was present. There was no complaint of sensory change or other symptoms to suggest neurologic disorder. There was no history of injury to the neck or to the involved extremity. Of interest was his habit, while filling out forms with many carbon copies, of pressing very firmly against the papers with his left hand to hold them in place while writing with his right hand. There were long periods of this activity during each working day. He had been doing this work nearly a year before symptoms developed.

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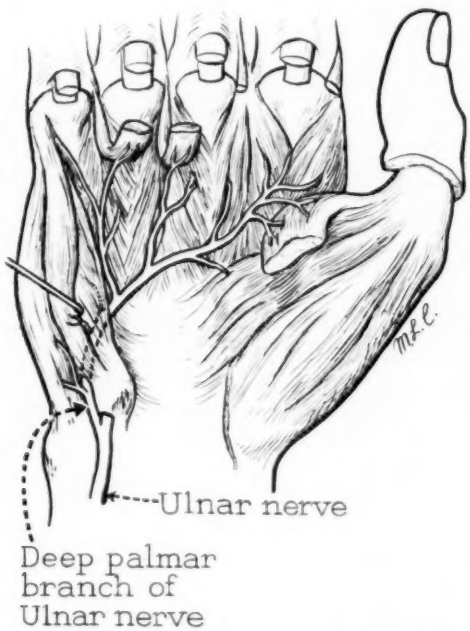
Examination disclosed interosseous atrophy. The hypothenar muscles felt soft and flabby but no atrophy was observed. Weakness was present in the interossei and adductor pollicis but was not as severe as that in Case 1. There were no sensory changes or other neurologic abnormalities. The hypothenar muscles were of normal strength.

The patient was advised to discontinue his activity involving pressure against the left hypothenar eminence, and after one and one-half years strength in the hand has improved and there has been some decrease in the amount of atrophy.

ANATOMICAL CONSIDERATIONS

In the distal forearm the ulnar nerve divides into a dorsal sensory branch and a volar branch, which runs to the wrist, where it crosses the transverse carpal ligament and lateral to the pisiform bone divides into a superficial and a deep palmar branch. The superficial branch supplies sensation to the palmar portion of the little finger and adjacent ring finger and also supplies the palmaris brevis muscle. The deep branch is a purely motor nerve and travels between the abductor digiti quinti and the flexor digiti quinti brevis. It passes through the opponens digiti quinti to reach the deep surface of the flexor tendons. It supplies the abductor digiti quinti, opponens digiti quinti, flexor digiti quinti brevis, the third and fourth lumbricales, the interossei, the adductor of the thumb, and the medial head of the flexor pollicis brevis.



Deep palmar branch of the ulnar nerve supplying the hypothenar muscles, interossei, and adductor pollicis.

It is thus evident that any lesion of the peripheral ulnar nerve in which sensation is intact is most apt to occur through changes distal to the superficial palmar branch of the ulnar nerve. To cause paresis of all muscles supplied by the ulnar nerve, it must rest in the short interval between the separation of the superficial sensory branch of the ulnar nerve and the point where the deep branch divides to supply individual muscles. As Hunt emphasizes, this short section of nerve lies on the outer side of the pisiform bone and passes downward, backward, and outward, winding beneath the hook of the unciform bone to reach the deeper structures of the palm.

COMMENT

The syndrome of neuritis of the deep palmar branch of the ulnar nerve must occur frequently despite the paucity of reports in the literature. As most writers on the subject have emphasized, the diagnosis can be easily overlooked unless the anatomy of the ulnar nerve is known to the doctor. The essential mechanism of this disorder was first reported by Hunt in a series of papers * in which he reported six patients. Harris [6] and Worster-Drought [7] in 1929 described additional cases. More recently, Bakke and Wolff [8] presented a patient and demonstrated by injection of hypertonic saline into the atrophic adductor pollicis that there was impaired sensitivity in the involved musculature despite the absence of cutaneous sensory disturbance. They suggested this as a procedure to differentiate between a neuritis and a degenerative myopathy or atrophy. Russell and Whitty [9] described five patients with neuritis of the deep palmar branch of the ulnar nerve in whom the hypothenar muscles were unaffected. This is not difficult to explain from an ana-

* References 1 and 3 through 5.

tomic standpoint, for the nerves supplying the hypothenar muscles leave the main nerve first and if the pressure were exerted in the deep palmar nerve beyond this point, only the interossei and adductor pollicis would be expected to be involved. The patients presented in this paper disclosed only minimal evidence of involvement of the hypothenar eminence. This would seem to indicate that the nerves supplying the hypothenar musculature were compressed, but not to the extent of the main deep palmar nerve trunk.

This disorder commonly occurs among persons in occupations involving heavy use of the hands, for example, machinists and metal polishers. The duration of time that pressure on the hand must be maintained to produce the syndrome varies widely in the reported cases. Russell and Whitty describe the syndrome occurring after only a transient pressure on the hand during a motorcycle trip in one case and a heavy day's gardening in another. In these, as in several other reported cases, evidence to suggest pressure neuritis was more subtle and could easily be overlooked unless the disorder was considered and careful inquiry made. Naturally, the differential diagnosis from a more serious degenerative disease must be considered when no sensory changes exist. The diagnosis of a relatively benign pressure neuritis of the ulnar nerve will allow the physician to give a reassuring prognosis to the patient and will also make the physician aware of the necessity for advising the patient to avoid further aggravation.

SUMMARY

Two patients with pressure neuritis of the deep palmar branch of the ulnar nerve are presented. In both patients a prolonged history of pressure against the hypothenar eminence could be elicited.

In both patients atrophy and weakness of the musculature of the ulnar nerve were observed without any attendant superficial sensory disturbance. The interossei and adductor pollicis were most affected, with only minimal involvement of the hypothenar musculature.

Despite the surprisingly few cases recorded in the literature, the syndrome must occur frequently. Awareness of its existence and of the anatomy of the ulnar nerve in the hand will undoubtedly result in more frequent diagnosis of neuritis of the deep palmar branch of the ulnar nerve. The possibility of an incorrect diagnosis of more serious degenerative motor disease would be lessened thereby.

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EFFECTS OF SUBCORTICAL LESIONS ON CORTICAL ELECTROENCEPHALOGRAM IN CATS

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SUBCORTICAL mechanisms which influence the electrical activity of the cerebral cortex have been widely investigated since the earlier work of Bremer * and Dempsey and Morison,[3] by Jasper and coworker,[4] Moruzzi and Magoun [5] and others. "Activation," or the evocation of an alerting effect on cortical potentials by stimulation of the reticular formation and hypothalamus, and evocation of recruiting responses by stimulation of reticular formation, thalamus, and some basal ganglionic structures have been extensively studied, especially by the groups of Magoun and Jasper. It has been shown, on the contrary, that suitable lesions in the hypothalamus and thalamus and extensive destruction of upper midbrain tegmentum profoundly affect spontaneous cortical potential patterns and produce behavior changes in animals and man (Ingram and associates,[6] Lindsley and associates,[7] Meyer and Hunter,[8] and Baird and associates [9]). The impulses producing activation apparently pass from reticular formation and hypothalamus by way of the internal capsule (Starzl, Taylor, and Magoun [10]), and possibly also by way of the so-called diffuse thalamic projection system, which mediates cortical recruiting responses. In the series of experiments to be presented here the effects of lesions in various parts of the thalamus, internal capsule, and caudate nucleus, and, to some extent, in the midbrain, on cortical potential patterns were studied.

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* References 1 and 2.

METHODS

Electrolytic lesions were produced stereotactically in selected regions of the thalamus, midbrain, internal capsule, and caudate nucleus in 35 cats. Postoperative observations of general behavior and responsiveness were made over periods ranging from one week to several months.

Cortical potentials were recorded through silver electrodes fastened into holes in the skull with acrylic plastic, the lead wires being soldered to the electrodes, which were in contact with the dura in either the frontal or the occipital region. These leads were placed in a preliminary operation. Usually eight contact points were available. A four-channel electroencephalograph was used for most observations; a Grass Model III eight-channel instrument and a low-frequency analyzer were, in some instances, also employed in recording cortical potentials.

After implantation of the electrodes and operative healing, several prelesion EEG's were taken, at intervals of several days, until it was certain the potential patterns were stable and sufficient information as to bilateral matching was secured. The animals were then reoperated on under pentobarbital (Nembutal) anesthesia, and the lesions were produced, using a craniotomy opening prepared at the time of the first operation. Recovery was usually rapid. Records were taken soon after recovery from the anesthesia and at intervals thereafter until normal potentials appeared or until the postoperative patterns stabilized. These recording periods were long enough to permit the animal to

become adjusted to the procedure, even to the point of drowsiness or sleep, and the effects of auditory and visual stimuli were observed. During the recording period the cat remained in a familiar cage, and an effort was made to schedule the observations for approximately the same time of day.

At the conclusion of the experiment the cat was killed, and the position and extent of the lesion were carefully analyzed microscopically.

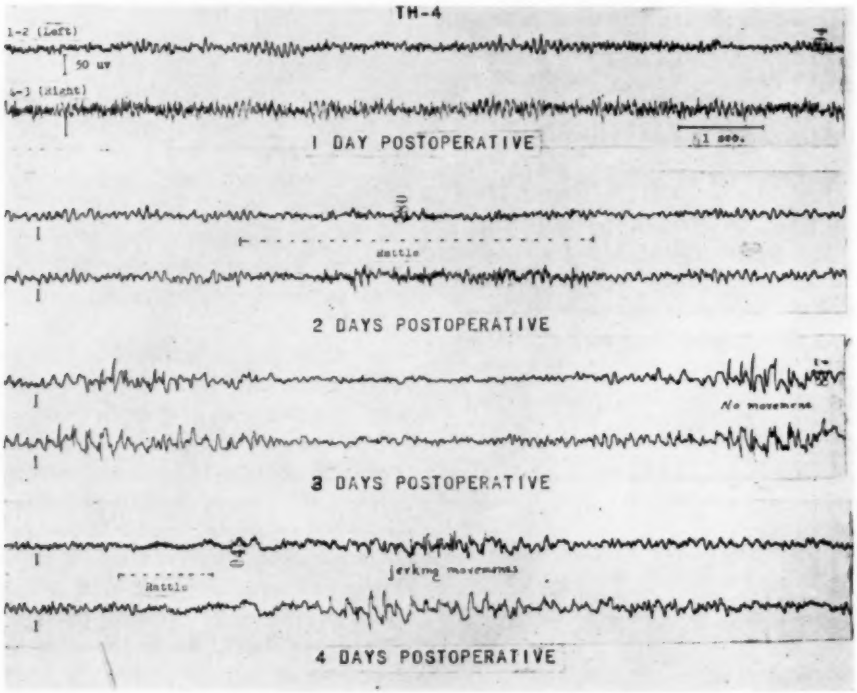
OBSERVATIONS

It is perhaps an aphorism to remark that experimental lesions satisfactorily restricted to a relatively small area or structure in an animal brain are rather rare. Neighboring structures are involved with distressing frequency, and even a so-called "pure" lesion is usually complicated by the implication of fibers of passage. In the following account the transgressions of our lesions will be indicated, but in some cases the weight of evidence will indicate a principal role for a certain structure. However, it seems best to describe the lesions and their effects in terms of the region involved. Thus, a lesion of the region of the intralaminar nuclei may include some neighboring cell groups, and since the neighboring effects vary from animal to animal, the evidence implicating one structure in a certain change in the EEG may be developed by a process of exclusion.

1. *Lesions of the Midbrain.*—Although the effects of large lesions of the midbrain on the EEG and behavior have been well described for acute and chronic preparations by Magoun and his associates, it was thought well to produce a few lesions in this region, especially with reference to asymmetrical effects on cortical activity.

Lesions were made in this region in five cats. In Cat 1 the damaged area extended

Fig. 1. (Cat 4).—Anterior, bilateral leads. Records from top down:
(1) Fair bilateral matching, without unusual slowing.
(2) Stimulation leading to low-voltage fast "alert" EEG; some spikes appearing on right.
(3) Spontaneous spikes, without associated movements, also appearing.
(4) "Alerting" with stimulation; this is followed by spiking and clonic jerking.



from the midline 5.5 mm. to the left and from the aqueduct to the interpeduncular region, destroying the left red nucleus, medial longitudinal fasciculus, central tegmental fasciculus, and related reticular formation, with some damage to the medial lemniscus. The animal showed the usual forced movement and spasticity associated with lesions in this region, but recovered well. The EEG showed initial intermediate slow activity in the left hemisphere, followed by increased rhythmicity on the left. Spontaneous activation was clearer on the right for some days, although both sides showed the alert pattern. By the 12th day bilateral synchrony was restored and further effects of the lesion on the EEG were not apparent.

In Cat 4 there were bilateral symmetrical lesions destroying the red nuclei and extending from the base dorsalward to the

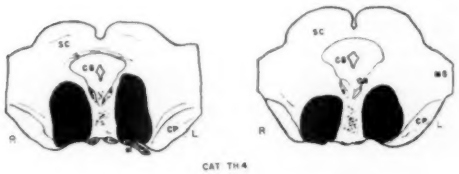


Fig. 2.—Drawing of midbrain lesions in Cat 4. For EEG see Figure 1.

level of the aqueduct, impinging very slightly upon the central gray matter (Fig. 2). The lesions were each about 3 mm. across and were separated by about 2 mm. of normal reticular formation. Postoperatively there was hypertonicity and tendency to drowsiness. The EEG seemed fairly normal, and alerting could be elicited. By the fourth day spontaneous spikes appeared, which were accompanied by slight myoclonic jerking (Fig. 1).

Cat 5 had lesions in the left reticular formation between the red nucleus and the medial geniculate nucleus, extending dorsoventrally from just above the peduncle to the level of the central gray matter. The medial lemniscus and spinothalamic tract were almost completely interrupted. Although the EEG showed some preoperative bilateral asymmetry, after operation there was increased slow activity on the left, especially when the cat appeared to be relaxed, with some bilateral spike activity. The left slow activity persisted to some extent for 22 days, although much bilaterally synchronous normal alpha activity was seen, and there was not much bilateral difference in frequency according to analyzer records at this time. The paroxysmal spiking was absent after one week.

The lesion in Cat 12 was large and bilateral, measuring 11 mm. across and extending from the base into the central gray matter (Fig. 5). The medial portions of both cerebral peduncles were damaged and considerable reticular formation was destroyed, more on the right than on the left. Postoperatively there was forced movement and spasticity, which was lost during sleep. Forced feeding was necessary. The EEG showed initial intermediate slow rhythms after operation, with good alert patterns evocable. There was occasional paroxysmal activity about one week postoperatively. While bilateral matching became fair, slower frequencies were present on the left. The animal was often difficult to arouse when asleep, but when aroused the EEG was of the alert type. At times the EEG appeared fairly normal (Figs. 3 and 4).

In one cat a small lesion involved the anterolateral part of the left superior colliculus and the brachium of the superior colliculus. There were no significant EEG changes, with the possible exception of an amplitude asymmetry, greater on the left than on the right.

2. Lesions of Posterior Ventrolateral Region of the Thalamus.—In four cats unilateral lesions were made in the so-called somesthetic relay, or projection nuclei. These lesions were less complicated by involvement of neighboring structures than is usual, and hence the results may be very significant. In two cases the overflow involved only the nucleus lateralis posterior slightly in each instance and a limited area of the reticular nucleus in one. In another case the chief external damage was to the ventromedial, ventrolateral, and lateralis posterior nuclei.

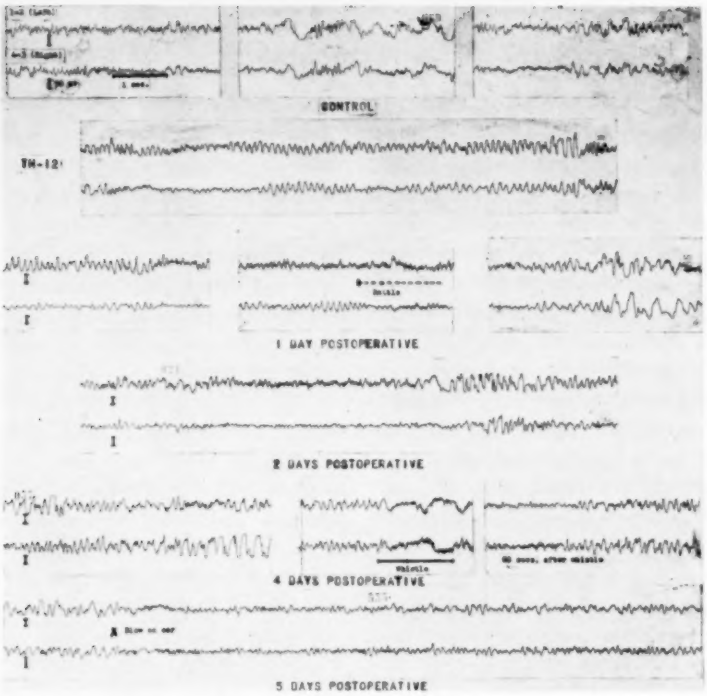
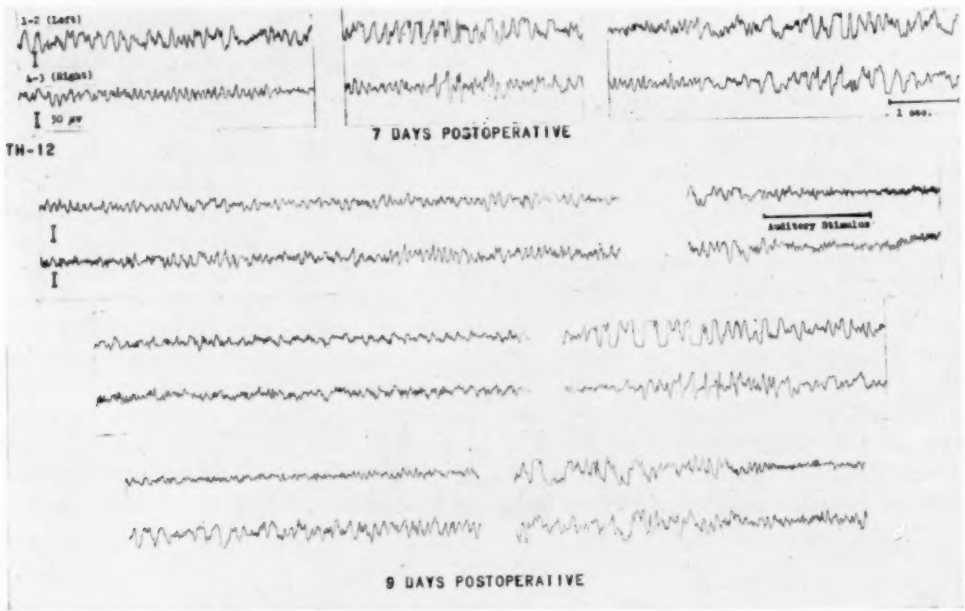


Fig. 3. (Cat 12).—Control record (top): Bilateral matching is good from the anterior leads, including sleep spindles (middle). On the first postoperative day there is a good deal of variability in the left and the right hemisphere activity, in general suggesting "more free-running activity" in the left hemisphere than the right, but exceptions can be seen. Two days postoperatively there is spiky activity on the left, and again in the "free-running activity." Four days postoperatively there is a fast variant wave and spike formation in the right hemisphere; bilateral alerting to strong auditory stimulation appears, with perhaps earlier recovery in the right hemisphere than in the left. Five days postoperatively a noxious stimulus alerts the animal from a drowsy EEG, with development of slow activity earlier in the left hemisphere than in the right.

Fig. 4 (Cat 12).—EEG's shown at seven and nine days postoperatively. Lateralized slow activity is present at seven days, as well as bilateral asynchronous, sharp and spiky activity. At nine days there is a good deal of variability, as may be observed in the six samples of records: reasonable bilateral matching; bilateral "alerting"; unilateral left slow waves; paroxysmal slow waves and spikes appearing asynchronously on left and right; unilateral slow waves on right; spontaneous alerting, bilaterally.



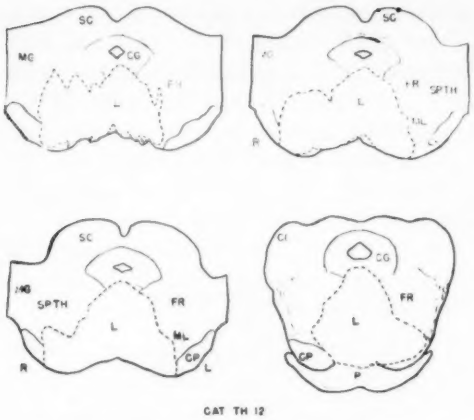


Fig. 5.—Drawings of midbrain lesions in Cat 12. For EEG see Figures 3 and 4.

In another some intralaminar damage occurred. These animals showed diminished sensitivity to pain stimuli on the side of the head and body opposite the lesions. The cases with the "purest" lesions showed little or no change in EEG in the ipsilateral cortex. In one case there was slowed activity for a few days only. Lowered frequencies persisted longest in the one instance in which there was incidental damage to the nucleus centralis medialis and the nucleus paracentralis. It can be stated with some confidence that lesions of the posteroventral part of the lateral thalamic group do not alter the EEG in a lasting way.

3. Lesions in Region of the Intralaminar Nuclei.—The nucleus centralis lateralis, nucleus paracentralis, nucleus centralis medialis, and centrum medianum are included in this region. It is obvious that lesions causing extensive damage to these nuclei are very likely to affect the dorsomedial nucleus, nucleus submedius, nucleus rhomboideus, and even part of the anterior nuclear complex. "Pure" lesions of any part of this group are rare; the centrum medianum is best suited for isolated injury. However, significant injury to this group in nine animals was always followed by change in the ipsilateral cortical potentials, which showed

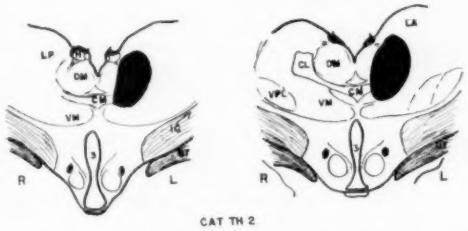
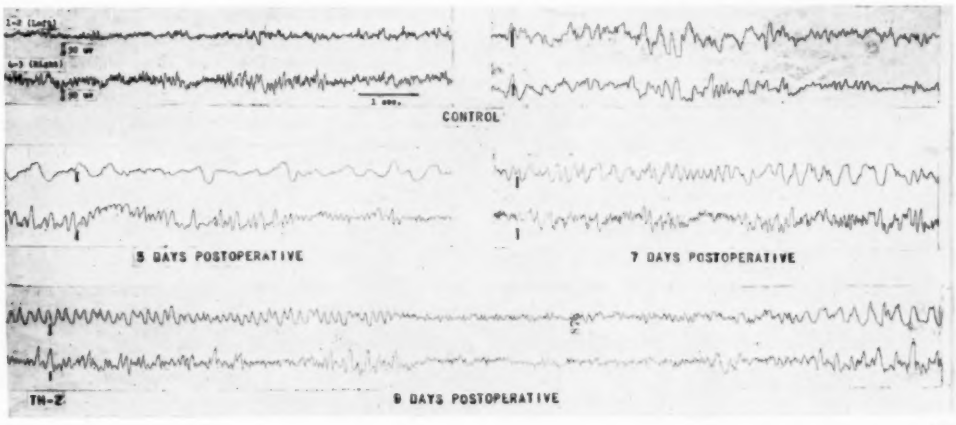


Fig. 7.—Drawings of lesions of intralaminar nuclei in Cat 2. For EEG, see Figure 6.

Fig. 6 (Cat 2).—Preoperative controls showing some bilateral dissimilarity when animal is awake but fairly good matching sleep activity. Five days after lesion of the intralaminar nuclei profound disruption of normal synchronous activity appears in the left hemisphere, the record being dominated by high-voltage very slow activity. Seven days postoperatively there is dramatic recovery toward preoperative rhythmicity, but slow activity still predominates. At the ninth postoperative day there is spontaneous bilateral low-voltage fast "alert" activity, but otherwise slow activity predominates in the left, although this is of increasing frequency. Frontal leads.



marked reduction in frequency (Figs. 6 and 7). This did not necessarily persist more than a few days. As a matter of fact, in cases in which the low frequencies persisted, damage to the anterior members of this group was not only extensive but involved other nuclei, so that one gains the impression that the volume of central thalamic tissue nearly completely destroyed with very little spread of the lesion. This was followed by frequency and amplitude asymmetry, with slow patterns on the left. There was delayed responsivity on the left, alerting being less easily elicited. These effects diminished, but persisted to some degree for at least three weeks.

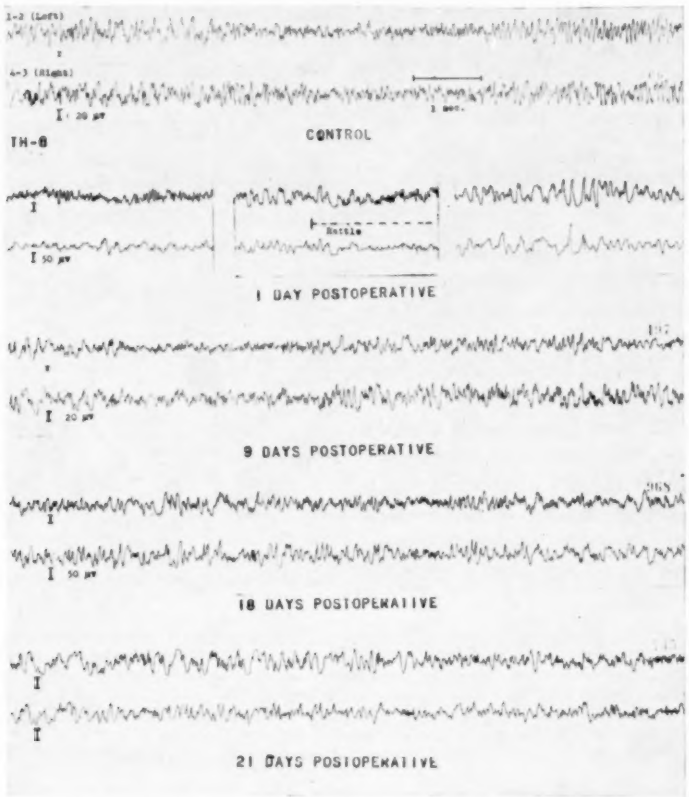


Fig. 8 (Cat 8).—Preoperative control EEG, showing fairly good bilateral matching. One day after a lesion was placed fairly well restricted to the left dorsomedial nucleus, there was bilateral dissimilarity, best seen in the alerting reaction, which tended to be more complete in the right hemisphere. There seemed to be an unusual amount of fast activity in the left hemisphere, with fairly good bilateral matching otherwise. At 9, 18, and 21 days postoperatively there was no dramatic difference between the left and the right hemisphere. Frontal leads.

destroyed may be the most important factor in altering the EEG. Our impression is that the nucleus centralis medialis and nucleus paracentralis have least to do with regulating the EEG; the nucleus centralis lateralis seems more important and the centrum medianum most important. In one instance (Cat 29) the last-mentioned nucleus was

4. *Lesions in Region of the Dorsomedial Nucleus.*—Extensive damage was produced in the dorsomedial nuclei in 10 cats. In most cases there was some extraneous injury, especially to the anterior and intralaminar nuclei. In all there was enhancement of the slower frequencies on the same side as the lesion (Figs. 8 and 9), and often an apparent

suppression of sleep spindle frequencies. This was true of occipital, as well as frontal, cortex. The altered frequencies were not necessarily persistent.

5. *Lesions in Region of the Anterior Nuclei.*—These lesions were also frequently complicated by involvement of nearby structures. However, in each of five instances the EEG showed postoperative asymmetry, with slow waves predominating on the side of operation. In an interesting case (Cat 10) a small lesion destroyed the left nucleus anterior dorsalis, with some damage to the nucleus anterior medialis, slight damage to the reticular nucleus, and some injury of the fornix (Fig. 11). The EEG showed immediate very slow activity in the left frontal cortex, which continued for the two weeks the animal was studied (Fig. 10). Alerting

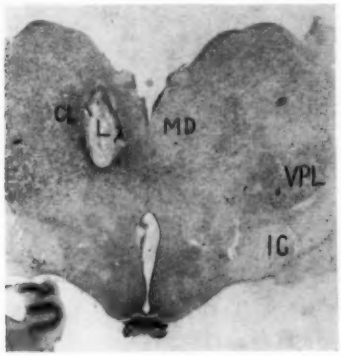


Fig. 9.—Photograph of lesion destroying the left dorsomedial nucleus in Cat 8. For EEG, see Figure 8. This lesion was fairly restricted.

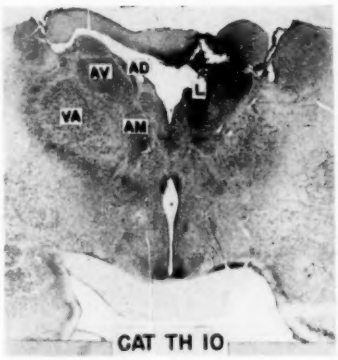
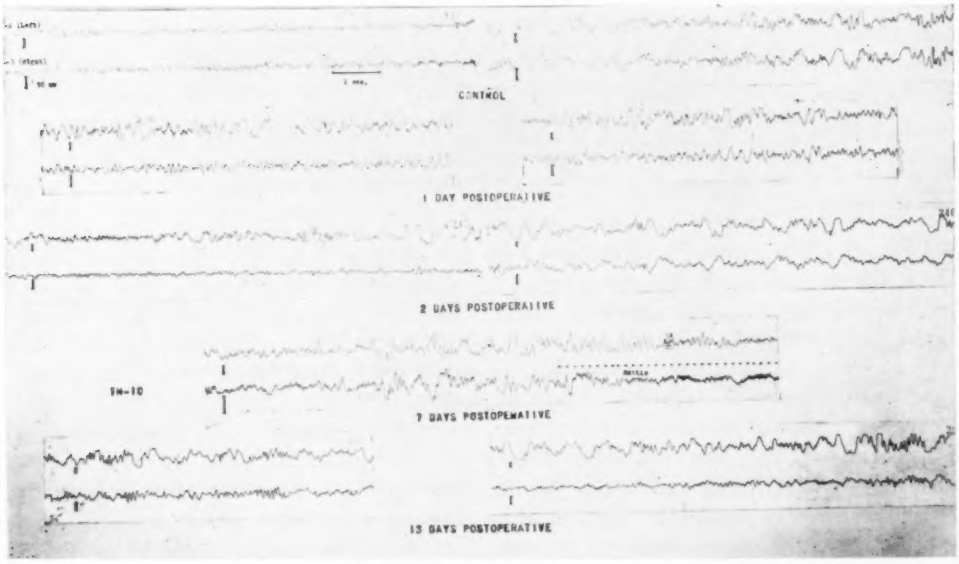


Fig. 11.—Photographs of lesion in anterior nuclei in Cat 10. For EEG, see Figure 10.

Fig. 10 (Cat 10).—Control EEG showing good bilateral matching. One day after a lesion was placed in the region of the left anterior thalamic nucleus there was preponderant slow activity ipsilateral to the lesion. This tended to persist on the second day but was less apparent in sleep. Seven days postoperatively, although fair bilateral matching obtained at times, the response to external stimulation was normal in the right hemisphere but was delayed or absent in the left hemisphere. The preponderance of slow activity is obvious on the 13th day. Frontal leads.



or activation of the left hemisphere was sometimes difficult to produce. In another case uncomplicated injury to the nucleus anterior ventralis produced ipsilateral slow potentials immediately after operation, but these did not persist. The same was true for another cat, in which the damage to the anterior group was restricted to the nucleus anterior medialis. The question arises as to whether or not anterior nucleus lesions produce their effects by interruption of fibers of passage on their way to the cortex.

ventralis posterolateralis was not followed by any significant change in the EEG. In another (Cat 34) severe damage to the nucleus ventralis anterior with slight encroachment upon the nearby internal capsule, but without affecting the anterior part of the reticular nucleus to any great extent, was followed by definite slowing of activity on the same side. This did not persist but returned to normal within three weeks. In the third case (Cat 27) marked injury to the left nucleus ventralis anterior was accom-

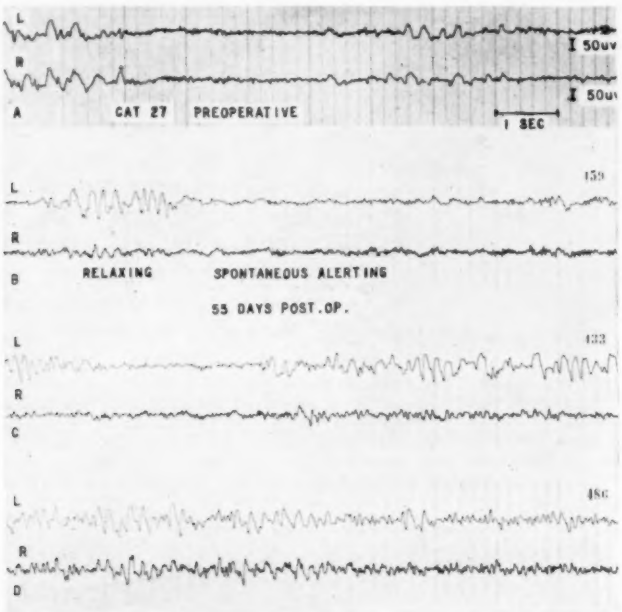


Fig. 12 (Cat 27).—Good preoperative bilateral matching (*A*). After an extensive lesion restricted to the left nucleus ventralis anterior and the reticular nucleus, there was fairly good bilateral matching when the cat was alert (*B*), but ipsilateral slow activity developed when the animal was relaxed (*C*). The bilateral dissimilarity was greatly reduced during sleep (*D*). Occipital cortical leads.

6. *Lesions in Region of the Nucleus Ventralis Anterior and the Reticular Nucleus.*—In three cats lesions in this area were complicated to a relatively minor degree by injury to other parts of the thalamus. A fourth had extensive damage to nonthalamic regions and showed marked behavior and EEG changes. This animal will be discussed separately later. In one case (Cat 22) a lesion affecting the posterior part of the reticular nucleus in the region of the nucleus

panied by destruction of the anterior portion of the left reticular nucleus, with no other significant damage. Postoperatively the animal was much more relaxed than before, and while the cat was awake there was greatly increased slow bursting on the left side, with some 3-per-second waves appearing (Fig. 12). When the cat was asleep, there was fairly good bilateral matching, as was true when it was sharply alert. In other words, the "slow" hemisphere could be alerted to

show low-voltage fast activity, whereas under ordinary postoperative conditions it was grossly different from the right. This condition persisted for at least two months. It is of interest in this case that these changes were apparent in the occipital leads. Evidently, effects transmitted through the anterior part of the thalamus may affect remote parts of the cortex, possibly through an indirect route. The importance of the ventral anterior and reticular nuclei as routes for elicitation of recruiting responses has been indicated by others, and it now appears that combined injury to these nuclei may have marked effects on cortical activity.

7. Lesions in Region of the Nucleus Ventralis Medialis.—Stimulation of this nucleus has also been found by Magoun and his group to evoke abundant recruiting responses. Lesions with minor extraneous involvement were produced in three cats (Cats 13, 17, and ST1); in two others (Cats 14 and 36) there were some complicating lesions. In one of the purer cases there was no change in the EEG; in the other two there was transient slowing on the same side as the lesion. In no case did EEG changes persist into a chronic stage. Apparently this region is not as important from the standpoint of regulation of the EEG as the nucleus ventralis anterior and the reticular nucleus.

8. *Lesions of the Caudate Nucleus.*—Four cats were in this group, in one case the caudate lesion being complicated by slight injury to the nucleus anterior ventralis. In no case was there a continuing change in the EEG. In three cases initially slower frequencies appeared ipsilaterally, but later became normal. In one instance there was lowered voltage on the side of operation. The caudate nucleus has also been implicated as a route for recruiting impulses (Shimamoto and Verzeano [11]), and the transient changes in EEG we have observed might support this idea. There was not complete destruction of the caudate nucleus in any of our cats, but the lesions were restricted to the caudal part of the head of the nucleus. This must be considered in interpreting our results. However, these results are not consistent with Droogleever Fortuyn's [12] statement that lesions of the caudate nucleus enhance cortical activity.

9. *Lesions in the Internal Capsule.*—These were relatively free from extraneous damage, although there was injury to the putamen in two cats, a small area of softening in the nucleus ventralis anterior in one, and some damage to the lateral nucleus in one. These lesions were on the right at the thalamic level; two were anteriorly placed, two more posteriorly. The animals with the more anterior lesions showed practically no motor disturbance; the posterior one showed circling to the right, loss of placing reactions on the left, and spasticity, most evident on the left. After the anterior lesions were made there was no change in the EEG in one case. In general the same was true for the other, but spindle bursts appeared to be more frequent on the right and it was a question whether this change was due to suppression of spindling on the left. This cat also showed on the first postoperative day a reduction in amplitude on the right.

Postoperative records in the cats with more posterior lesions, however, showed new, very slow frequencies in the right hemisphere, especially when the animal was at rest and relaxed. In one cat (Cat 42) there was marked suppression of activity on the right (Fig. 13), except for some slow waves, and occasional spike and wave combinations appeared at a frequency of 4 to 5 per second. It is of interest that these lesions were better placed to damage fiber connections arising in the reticular formation, and perhaps from the hypothalamus, than were the anterior lesions. They extended caudalward nearly to the level of the mammillary bodies and the entopeduncular nuclei were, of course, involved.

Damage to the putamen in the two anterior lesions with little, if any, change in the EEG tends to indicate that this structure probably has little relationship to cortical activity.

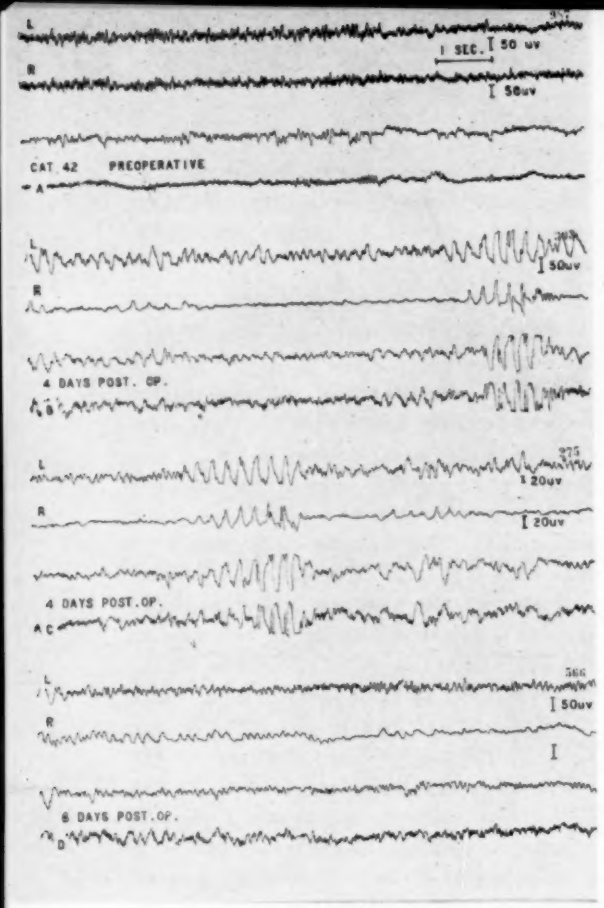


Fig. 13 (Cat 42).—Preoperative records showing good bilateral matching (*A*). Four days after a lesion in the posterior part of the right internal capsule there was apparent suppression of activity in the right hemisphere, with some bursts of 4 to 5 per-second waves in both hemispheres, and some "wave-and-spike" activity at 4 and 5 per second (*B* and *C*). On the sixth day the suppression on the right continued, with some bursts of slow waves. Channels 1 and 2, frontal cortical leads; Channel 3, left to right, lateral; Channel 4, left to right, medial.

COMMENT

Kennard[13] described slow cortical potential patterns in monkeys following thalamic lesions. These lesions were massive, however, and no localization was attempted. Effects of bilateral lesions of certain thalamic structures upon the EEG have been reported by Meyer and Hunter.[8] Behavior changes following lesions of the region of the upper end of the mammillothalamic tracts, including apathetic and akinetic states, were accompanied by EEG patterns showing slow waves similar to those of sleep. Cortical activation was not as readily produced by sensory stimulation in these cats as in normal ones. Since the lesions in our present series were nearly all unilateral, we can make little comment. However, the similarity between their abnormal EEG patterns and those appearing in our cats after extensive lesions may be noted. As to behavior changes, we have not seen anything resembling those which Meyer and Hunter describe, except with large lesions of the hypothalamus and of the preoptic areas. In observations not included in the present series, in which the mammillary bodies were destroyed with little, if any, other damage, no significant behavior change was observed (five cases), and the same was true when the mammillothalamic tracts were destroyed in the ventral region of the thalamus.

However, one animal in our present series (Cat 35) did show a remarkable alteration in behavior. After recovering from anesthesia, this cat appeared drowsy but crouched or stood with head held high. There was some spasticity. Either spontaneously or when aroused it paced around and around in its cage, or when free it would walk until stopped by some obstruction and then stand motionless. It followed moving objects and noticed noises. There was some obstinate progression, and it was able to climb out of a high cardboard box by walking up the corner. These periods of activity alternated with statuesque sitting or standing, and the cat was not seen in a normal comfortable sleep position, although she appeared to sleep while crouching. Feeding was very poor. The cat's demeanor gave an impression of remoteness and abstraction, but she responded to most types of stimulation. There was a dramatic change in the EEG, which became very slow bilaterally. The dominant pattern was irregular bursting at slow frequencies of 4 sec. to 6 sec. After the second postoperative day, alerting was readily produced. This animal had large symmetrical lesions, which reached their most ventral point posteriorly at the anterodorsal edge of the optic tract lateral to the infundibulum, and anteriorly in the preoptic areas at the posterior margin of the anterior commissure. Dorsally the lesion largely destroyed the nuclei ventralis anterior and damaged the

lateral part of the nucleus anterior medialis. There was slight damage to the nucleus lateralis posterior and the nucleus ventralis lateralis. The medial portions of the internal capsules were destroyed from the level of the anterior commissure almost to the subthalamic nuclei. The anterior portions of the lateral hypothalamic areas were destroyed caudally as far as the supraoptic nuclei, which were mostly intact, and the right fornix was interrupted. Other thalamic and hypothalamic structures appeared intact. In this case, profound behavior change and a bizarre EEG followed lesions of the anterior ventral part of the thalamus, the preoptic area, and the anterior lateral hypothalamus. The anterior nuclear complex was not seriously affected.

Transitory catalepsy and reduced reactivity were noted in cats following extensive lesions of the anterior nuclei by Baird, Guidetti, Reyes, Wycis, and Spiegel.[9] Koella and Gellhorn,[14] however, found that lesions of the anterior and dorsomedial thalamus did not depress the activation of the cortex ordinarily induced by nociceptive stimulation and CO_2. Unilateral lesions which were effective in producing this depression covered such areas as the mesencephalic tegmentum, the posterior part of the hypothalamus, the centrum medianum, the intralaminar nuclei, the nucleus ventralis medialis, nucleus ventralis posteromedialis, nucleus ventralis lateralis, nucleus ventralis anterior and ventral parts of the reticular nucleus, and the base of the caudate nucleus. In general, as the authors say, these structures comprise the diencephalic part of Magoun's activating system. In other acute experiments Hanbery and Jasper[15] and Hanbery, Ajmone-Marsan, and Dilworth[16] have studied the effects of thalamic lesions on cortical responses to stimulation of the so-called diffuse projection system and found the pathways for such responses to be independent of the specific projection nuclei and the striatum. They also found that the nonspecific pathways probably utilize to greatest extent the nucleus ventralis anterior and the rostral pole of the reticular nucleus.

In general, the results of our experiments agree fairly well with the above. The most lasting changes in cortical activity were found with lesions involving the intralaminar nuclei, centrum medianum, nucleus ventralis anterior, and the rostral part of the reticular nucleus. In our series there are cases in which the lesions were restricted to the centrum medianum and to the nucleus ventralis anterior and neighboring reticularis, and in each instance the EEG changes were persistent for survival periods of three weeks to three months. It seems that on the basis of our experience lesions involving the so-called nonspecific thalamic structures plus the nucleus ventralis anterior are much more likely to produce lasting changes than those in the specific systems. Of the latter, lesions of the anterior and dorsomedial groups are most likely to produce transient changes. Lesions of the sensory relay portions of the ventral nuclear mass have usually not been associated with any change in spontaneous cortical activity. It may be noted that Spiegel, Wycis, and Umlauf[17] found only transient slowing of the rhythms of the EEG in cases of bilateral lesions in the dorsomedial nuclei in humans.

While the lesions which alter the EEG seem to involve extensively the diffuse projection mechanisms, these lesions do not greatly interfere with alerting or activation pathways. Alerting was depressed in the ipsilateral cortex in a very few instances, and in these cases the effect was transient. During strong alerting in response to vigorous stimulation or to environmental change, bilateral matching of cortical frequencies become good. Thus, while alerting impulses from the reticular system and hypothalamus may pass through the diffuse system, other pathways seem available, especially for extrinsic stimuli, as was indicated by Starzl, Taylor, and Magoun.[10] In this connection it may be noted that in our experience lesions in the posterior portion of the internal capsule seemed to produce definite change in the EEG, while lesions in more anterior regions of the capsule did not. The posterior portion appears to be that which is most

likely to convey corticipetal impulses from the reticular formation, hypothalamus, and ventromedial thalamus.

There is still little anatomic evidence as to pathways from the thalamic reticular system to the cortex.[18] Our observations support those investigators who believe that the anterior part of the reticular nucleus is the chief route by which impulses may be disseminated to all parts of the cortex. It will be recalled that marked changes in EEG were recorded from the occipital cortex when this region was destroyed. Droogleever Fortuyn[12] has suggested that the intralaminar nuclei project through the caudate nucleus, and Shimamoto and Verzeano[11] offer evidence that the latter is connected with the diffuse system. Kennard[13] observed a shift to slow frequencies in cortical activity after lesions of the caudate in monkeys. In our experiments relatively small portions of the caudate were destroyed, with only transient slowing effects on the EEG. Droogleever Fortuyn has also suggested that the centrum medianum projects by way of the putamen. However, in our experience lesions of the putamen have not modified the EEG significantly, although damage to centrum medianum may produce such alterations.

SUMMARY

Lesions were produced in selected regions of the thalamus, midbrain, internal capsule, and caudate nucleus in 35 cats. Cerebral cortical potential patterns were recorded with implanted electrodes before and after operation, without anesthesia or direct restraint. In general, the results were as follows:

1. After midbrain lesions there was increased slow activity, which returned to normal with restricted or unilateral lesions, but tended to persist with large or bilateral lesions. Significant amounts of reticular formation must be destroyed for changes to occur, and no change followed a lesion of the superior colliculus.

2. Lesions of the posterolateral part of the ventral nuclear group did not alter the EEG in a lasting way.

3. Lesions of the intralaminar nuclei produced slow activity in the ipsilateral cortex, which tended to be transient when the nucleus centralis medialis and nucleus paracentralis were involved. The changes were more persistent when the nucleus centralis lateralis was affected and most lasting when the centrum medianum was destroyed.

4. Lesions of the dorsomedial nucleus also enhanced the slower frequencies ipsilaterally, but these changes were not necessarily persistent.

5. Transient changes in activity followed lesions of the anterior nuclei.

6. Marked and persistent changes, with slow frequencies predominating, followed destruction of the nucleus ventralis anterior and the anterior part of the reticular nucleus, even affecting the occipital region of the cortex.

7. Transient changes in cortical activity followed lesions of the nucleus ventralis medialis.

8. Restricted lesions of the caudate nucleus were followed by mild and transient slow patterns. No change followed large lesions of the putamen.

9. Lesions of the posterior part of the internal capsule caused marked changes in cortical activity, while anterior ones did not.

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ADDENDUM

The following Addendum was received from Dr. Bruno W. Volk after the article "'Protein Profile' in Multiple Sclerosis," by Dr. Bruno W. Volk, Mr. Abraham Saifer, Dr. Abraham M. Rabiner, and Mr. Irwin Oreskes (January, 1955, issue, pp. 66-75) was on the presses.

ADDENDUM

Since this paper was submitted for publication, an article by Bernsohn and Cochrane entitled "Electrophoretic Fractionation of Serum Protein in Multiple Sclerosis" appeared in the *Proceedings of the Society for Experimental Biology and Medicine* (**86**:540-542, 1954), in which these authors confirmed our previously reported findings with respect to serum protein fraction in this disease (see Reference 1), except for the fact that many of our cases showed an increase in the beta globulin fraction, as well as in the alpha-2 globulin fraction.

ENCEPHALITIS FOLLOWING SMALLPOX VACCINATION

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MORRIS GREENBERG, M.D.
and
ROSA ARONOFF, M.D., New York

VACCINATION against smallpox carries with it a known risk of postvaccination encephalitis. The rate of incidence of this complication is not constant. The numerous reports of encephalitis following smallpox vaccination show that the incidence varies not only in different localities but also in the same locality in different years. In Tyrol, for instance, a rate of 1 case of encephalitis to 641 vaccinations was reported in 1929, while an incidence ratio of 1 : 4570 was observed in 1927.[1] In the United States, 1 case in 350 vaccinations occurred in the years 1928 to 1930, but a ratio of 1 : 1000 was recorded in a large city in 1930.[2]

A presumptive diagnosis of postvaccination encephalitis is usually made on the basis of the onset, 7 to 14 days after vaccination, of an acute illness, with fever, headache, vomiting, change in the mental state, signs of meningeal irritation, paralyses, and other neurological findings. It is obvious that many unrelated conditions may manifest such a symptomatology and be diagnosed as postvaccination encephalitis. On the other hand, it is conceivable that some of the mild cases may escape recognition.

In April, 1947, after the appearance of several cases of smallpox in New York City, about 5,000,000 persons were vaccinated in the city and its suburbs.[3] A clinical diagnosis of postvaccination encephalitis was made in 49 cases; 8 of these patients died. Necropsies were performed in all eight cases. Gross findings immediately showed that in four cases death was due to unrelated diseases of the central nervous system (two patients died of tuberculous meningitis, one of brain tumor, and one of hypertensive vascular disease). There remained 45 cases with the diagnosis of postvaccination encephalitis, with four deaths. Necropsy in one of these cases was performed by one of us; the material on the other cases was made available to us through the courtesy of Dr. Thomas Gonzales, Chief Medical Examiner, Dr. Chester Brown,† pathologist of Lincoln Hospital, and Dr. George Sharnoff, pathologist of Mount Vernon Hospital. Microscopic examination of the brains showed that in two cases there was no encephalitis; in the remaining two cases there was encephalitis, but the picture differed morphologically from that of postvaccination encephalitis.

Necropsies were also performed on two infants who died without a clinical diagnosis of postvaccination encephalitis; microscopic examination of the brains in these cases showed encephalitis with some features similar to those seen in encephalitis of postvaccinal type.

The six cases are the subject of this report.

REPORT OF CASES

Cases with Clinical Diagnosis of Postvaccination Encephalitis

CASE 1.—M. H., a Negro woman 39 years old, was vaccinated on April 28. On April 29 she entered New York City Hospital for an elective hysterectomy and was operated upon on April 30, 1947, under spinal dibucaine (Nupercaine) anesthesia. She made a good recovery and was up and about on May 4. On May 5 she became lethargic and disoriented; the temperature was 102 F. On May 6 moderate opisthotonos developed, and she lapsed into coma. Her condition grew progressively worse, with the temperature rising to 105 F, and she died on May 10, six days after the onset of the neurological manifestations.

From the Pathologic Laboratories of the Willard Parker Hospital; the Bureau of Preventable Diseases, New York City Department of Health, and the Pathologic Laboratories of the Greenpoint Hospital, Brooklyn.

† Now deceased.

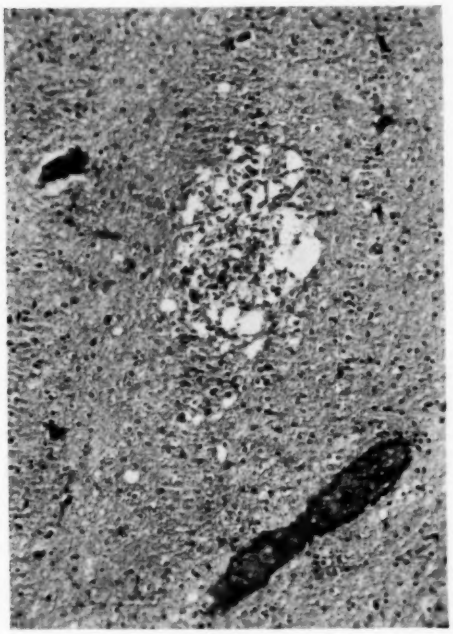
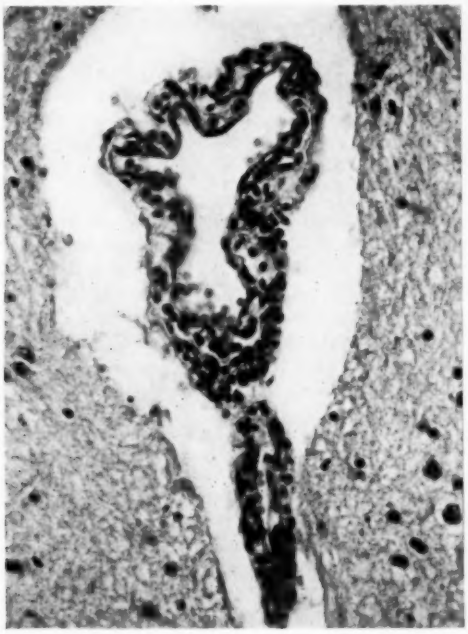


Fig. 1 (Case 1).—Coarse focal degeneration of myelin, not related to blood vessels, in the internal capsule. Slight lymphocytic infiltration of the wall of a vein at some distance from the degenerated area. Masson's trichrome stain; × 120.

Fig. 2 (Case 2).—Lymphocytic infiltration of the adventitia of a vein in the medulla. Hematoxylin and eosin stain; × 375.



The spinal fluid on two occasions showed 25 and 50 cells per cubic millimeter, chiefly mononuclears, was sterile, and showed normal chemical constituents.

The necropsy was performed by the Medical Examiner. The gross findings were healing vaccination lesion, recent hysterectomy, lobar pneumonia, adhesive leptomeningitis, and acute infectious encephalitis.

The brain weighed 1110 gm.

Microscopic examination of the brain showed small, discrete, round foci of coarse degeneration of myelin, not related to blood vessels, in the internal and external capsules (Fig. 1). The veins in the vicinity of such foci showed infiltration of the adventitia with lymphocytes one to two rows deep. A few pale nuclei of astrocytes and occasional nuclei of microgliocytes were present in the areas of demyelination. Two small foci of degeneration were found in the thalamus. There was no degeneration of the myelin in the white matter of the hemispheres or in the midbrain, pons, or medulla.

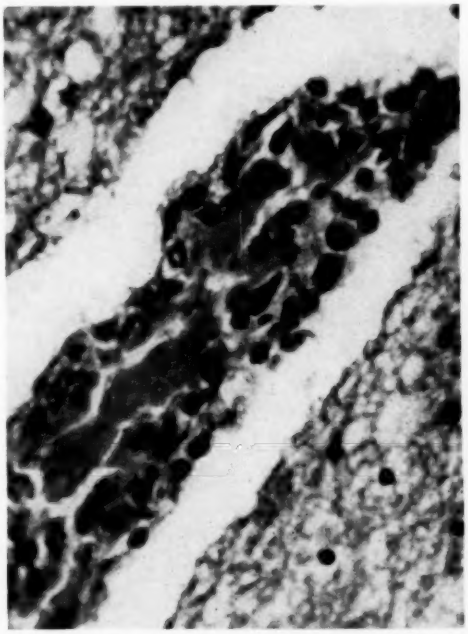


Fig. 3 (Case 5).—Large mononuclear cells infiltrating the adventitia of a vein in the midbrain. Similar cells are lined up against the endothelium in the lumen of the vein. Hematoxylin and eosin stain; × 700.

Most Betz cells in the motor cortex were ballooned by accumulation of lipochrome, with peripheral displacement of the nuclei and of the comminuted Nissl substance. A few venules in the gray and white matter in that area showed infiltration

of the adventitia with a single row of lymphocytes. Areas of old fibrous thickening were present in the pia-arachnoid of the cortex; one of them also contained a focus of polymorphonuclear leucocytes.

Diagnosis.—Atypical encephalitis with myelin damage, not characteristic of postvaccination encephalitis; old and recent leptomeningitis.

Case 2.—A. M., a white youth, 16 years old, was vaccinated on April 13, 1947, with a resultant good take. On April 23 he had a headache and fever. The next day the patient had convulsions and became incontinent of urine. He was admitted to the Greenpoint Hospital, where his reflexes were found

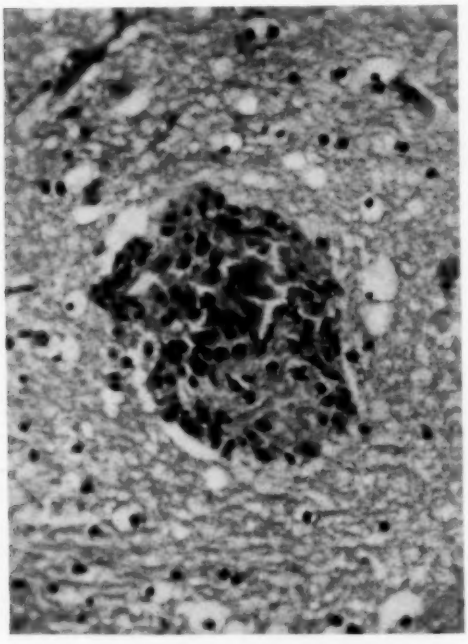


Fig. 4 (Case 5).—A vein in the striate body, showing partial thrombosis (lower portion), slight mononuclear infiltration of the adventitia, and intact extra-adventitial white matter. Hematoxylin and eosin stain; × 430.

to be normal and no nuchal rigidity was noted. During the following days the patient became delirious, then stuporous; his temperature rose to 108 F, and he died on April 28, two weeks after the vaccination and five days after the onset of the illness. The spinal fluid on two occasions showed 70 and 121 cells per cubic millimeter with 60% and 70% polymorphonuclear cells, respectively, and a slight elevation of globulin. Other findings, including the bacteriology and serology, were normal.

The gross necropsy findings were as follows: a dry scab of a recent vaccination and an old vaccination scar; congestion of the lungs and of all abdominal organs; edema and congestion of the brain.

The brain weighed 1450 gm. A piece of lumbar cord was obtained by the abdominal route.

Microscopic examination of the brain showed occasional groups of lymphocytes in the meninges of the sulci of the frontal cortex, at the root of one fifth cranial nerve, and at the nerve roots of the lumbar cord. A number of venules in the gray and white matter of the cortex, in the corpus callosum, in the medulla (Fig. 2), and in the anterior and posterior horns of the lumbar cord showed infiltration of the adventitia with one to three rows of lymphocytes. Minimal adventitial infiltration was also present in a few venules of the pons, of the substantia nigra, and around the aqueduct. A few calcific bodies were seen in the putamen. There was no loss of myelin. The ganglion cells of the pons and medulla were intact; others showed technical shrinkage, and their morphology could not be evaluated. A few small, loose microglial collections, not related to ganglion cells, were found in the lumbar cord. Some satellitosis was noted in the cortex and midbrain.

Diagnosis.—Encephalomyelitis without demyelination.

Case 3.—F. R., a Puerto Rican woman, 35 years old, was vaccinated on April 21, 1947. Four days later she had a slight fever, then became disoriented, drowsy, and stuporous. She was treated at home until May 8, when she was admitted to Lincoln Hospital. At the time of admission she had mask-like facies and incoherent speech and was disoriented. She had a bilateral Kernig sign, a positive Brudzinski sign, and nuchal rigidity. The course was downhill, and she died on May 11. There was no history of a take of the vaccination, and there was no postvaccination scar. The spinal fluid on one occasion contained 4 cells, per cubic millimeter, but on the following day the count showed 92 cells, with 82 lymphocytes.

The necropsy showed acute hepatitis, acute splenitis, fatty degeneration of the kidneys, hemorrhages in the lungs and kidneys, and petechiae in the aorta and renal pelves.

The brain was congested. Microscopically, a few minute extravasations of blood were seen, but there were no inflammatory or degenerative changes in the tissue available for examination.

Diagnosis.—Acute hepatitis; congestive encephalopathy.

Case 4.—A. M., a white man, 34 years old, a patient of Dr. Paul Sacerdote, was vaccinated on April 16 and felt well until April 25, when he suddenly developed severe headache, followed by convulsions. He was taken to the Mount Vernon Hospital, where he died within one hour. At necropsy the brain and all other organs showed marked con-

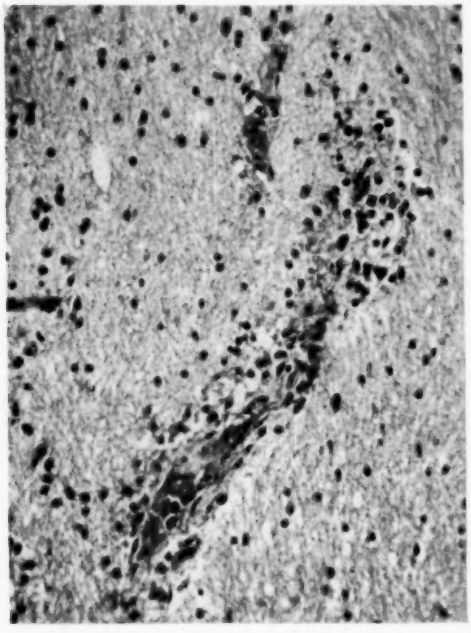


Fig. 5 (Case 5).—Early degeneration of the myelin and extra-adventitial infiltration (at the upper pole of the vein) in the corpus callosum. Hematoxylin and eosin stain; × 315.

gestion. Microscopic examination revealed a severe acute focal myocarditis, with mononuclear inflammatory foci. The brain showed congestion and occasional small petechial hemorrhages.

Diagnosis.—Acute focal myocarditis; congestive encephalopathy.

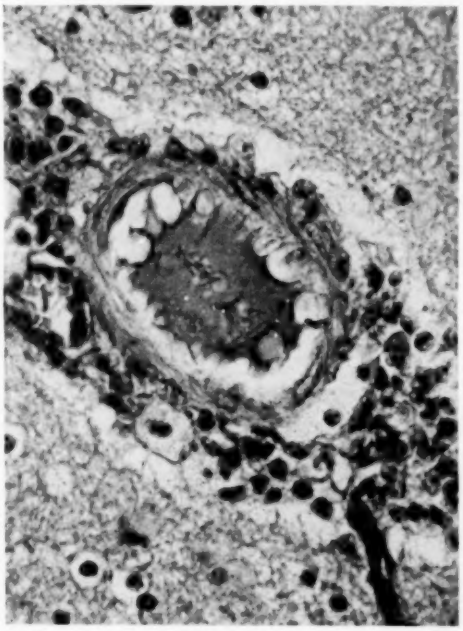
Cases Without Clinical Diagnosis of Post-vaccination Encephalitis

Case 5‡—R. S., a white male infant 8 months old, who had had eczema since the first month of life, was exposed to his vaccinated parents, who exhibited accelerated takes. On May 11, 1947, a confluent vesicular lesion was noted on one side of his face. Additional lesions appeared later on other parts of his body as umbilicated pustules. A diagnosis of vaccinia was made, and the child was admitted to the Willard Parker Hospital on May 16, with an eruption over the face, neck, and extremities and generalized lymphadenopathy. Later, large areas of the skin became denuded from scratching. The child's course was downhill. On the ninth day after the appearance of the pustular lesions, rolling of the eyes, horizontal nystagmus, and slight spasticity of the extremities were noted. The child died four hours after the appearance of these neurological manifestations. There was no examination of the spinal fluid. The blood count showed 12,800 white blood cells, with 85% neutrophiles and 15% lymphocytes.

Necropsy revealed generalized vaccinia, chronic eczema, dehydration, emaciation, and passive congestion of the internal organs. The meninges were edematous. The brain was pale and weighed 830 gm. A piece of lumbar cord was obtained by the abdominal route.

Microscopic sections of the brain and spinal cord showed a great many venules with adventitia infiltrated by one to three rows of large mononuclear cells and rare neutrophiles. Mononuclear cells were also present within the lumen of the venules, lined up or heaped up against the endothelium; some of these cells appeared to be entering the walls of the vessels (Fig. 3). Some of the veins showed partial obstruction of the lumen by deposits of amorphous granular material, probably deriving from platelets (Fig. 4). The greatest number of veins with infiltrated adventitia was found in the pons and midbrain, both in the gray and in the white matter. Other such vessels were present in the striate body, in the white matter of the hippocampus and the cerebellum, in the medulla, and in the lumbar cord, where they were located in the posterior horns, in the gray commissure, and in the posterior

Fig. 6 (Case 6).—Infiltration of the adventitia of an arteriole by large mononuclear cells. A large, "foamy" phagocyte is seen in the infiltrate. Left parietal region. Hematoxylin and eosin stain; × 520.



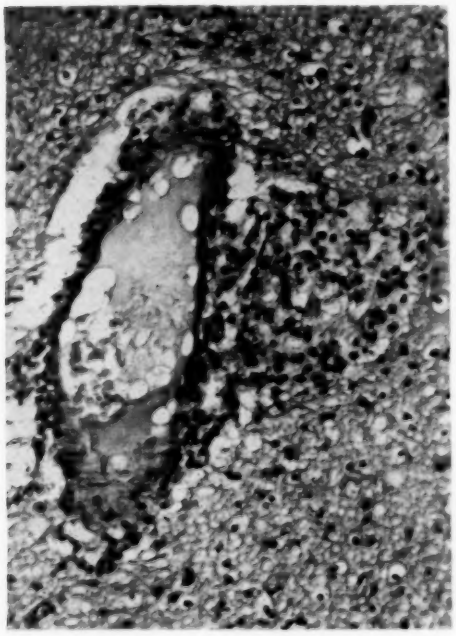
‡ A full clinical report on this case appeared in a paper by Mustard and Hedrick [4] as Case 2.

white column. Incipient, minimal breaking up of myelin, with some extra-adventitial infiltration by mononuclear cells, was found around several venules in the corpus callosum (Fig. 5). The adventitia of these venules showed no cellular infiltration. The ganglion cells showed no damage. Occasional small perivascular extravasations of red blood cells were seen in various parts of the brain.

Diagnosis.—Chronic eczema; generalized vaccinia; encephalomyelitis with incipient myelin damage (possibly early postvaccination encephalitis).

Case 6.—L. Q., a Puerto Rican girl 5½ months old, was admitted to the Willard Parker Hospital on May 19, 1947, with pertussis of three weeks' duration. The child had an elevated temperature and frequent, severe paroxysms of cough. Pneumonia was diagnosed, and Hemophilus pertussis was isolated from the nasopharynx. On May 27 the child became drowsy, had generalized twitchings, and a temperature of 107 F. On the following days she became comatose, with the temperature ranging between 98.6 and 103 F. Blood counts showed 96,000 and 27,000 white blood cells, with lymphocytosis. She died on June 6, with a terminal rise of temperature to 107 F. The clinical diagnosis was pertussis, bronchopneumonia, and pertussis encephalopathy. The spinal fluid on May 28 contained 5 cells and was chemically normal. After the microscopic examination of the brain was completed and encephalitis with perivascular glial collections was demonstrated, further inquiries from the family established that the child had been vaccinated one month prior to admission to the hospital, or about seven weeks before death. No statement about the character of the take was available, and no recent scar was mentioned in the history.

Fig. 7. (Case 6).—Eccentric extra-adventitial infiltrate in the left motor region. Hematoxylin and eosin stain; × 210.



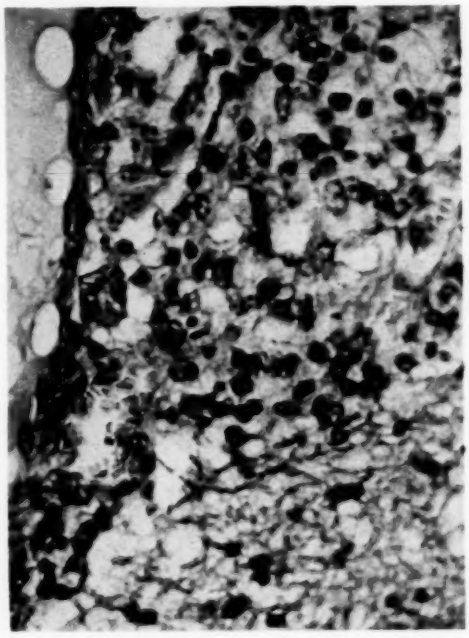


Fig. 8 (Case 6).—Detail from Figure 7, showing large mononuclear cells, a few lymphocytes, and occasional stellate glia-like cells in the extra-adventitial infiltrate. Scattered large, deep-staining astrocytes are seen in the white matter below the infiltrate. Hematoxylin and eosin stain; × 430.

Necropsy showed bronchitis with numerous mucus plugs in the lumen; areas of atelectasis and areas of pneumonia, predominantly peribronchial in distribution; lymphoid depletion of the spleen, and incidental atrophy of the thymus.

The brain weighed 800 gm. and showed edema and congestion of the meninges, moderate flattening of the convolutions, and slight congestion of the gray and white matter.

Microscopically, the meninges showed considerable edema and occasional small extravasations of red blood cells. The veins and capillaries of the brains were markedly congested, especially in the white matter. No anoxemic changes were found in the Purkinje cells of the cerebellum or in the pyramids of the hippocampus. Cellular infiltration of the adventitia and some extra-adventitial infiltration of the white matter were found around three veins of the left motor area, two arteries of the left

parietal lobe, and two veins of the right frontal lobe. The adventitial infiltrates consisted of a small number of lymphocytes, some larger cells with dark cytoplasm and dark or vesicular nuclei, and occasional phagocytes with foamy cytoplasm (Fig 6). The extra-adventitial tissue was loose and was infiltrated by cells with small dark nuclei and by larger cells with poorly staining, apparently stellate bodies and pale, vesicular nuclei (Figs. 7 and 8). On the periphery, scattered large astrocytes, with cytoplasm well stained in eosin, were present. There was no degeneration of the white matter, in which the fibers apparently were pushed aside by the infiltrating cells. There was a diffuse increase in the number of eosin-stained large astrocytes throughout the white matter. A slight marginal gliosis was present in the cortex, in the depth of the sulci.

Diagnosis.—Pertussis; bronchitis; areas of atelectasis and of peribronchial pneumonia; residual encephalitis, possibly of postvaccination origin.

COMMENT

The microscopic pictures in the cases of encephalitis (Cases 1, 2, 5, and 6) were different, and the findings had to be analyzed from the point of view of their resemblance or dissimilarity to the microscopic picture in postvaccination encephalitis as established by Turnbull and McIntosh.[5] These authors described the microscopic findings in seven cases. Six of their patients died in the acute stage of postvaccination encephalitis; the seventh, in the subacute stage, on the 29th day of illness and the 18th day of neurological manifestations. In the acute stage the changes were (1) extra-adventitial collections of glia cells and neutrophiles in the gray and white matter of the brain and spinal cord; (2) infiltration of the vascular adventitia with a narrow sleeve of predominantly mononuclear cells; (3) zones of "softening" of perivascular myelin (Perdrau[6] and the majority of subsequent authors refer to this process as "demyelination"), with only a few glial cells and neutrophiles in the degenerated areas, and (4) hyaline or fibrinous thrombi in some blood vessels. The lesions were present in all parts of the brain and cord but were most numerous in the pons and the lumbar and sacral cord. The ganglion cells showed little, if any, change and preserved their angularity. This feature is also corroborated by Perdrau.

Case 1 in this series, despite the presence of damage of myelin, could not be classified as one of postvaccination encephalitis. The coarse degeneration of myelin was not perivascular in distribution and was limited to the white matter of the striate body. The pons was intact. No extra-adventitial infiltrates were found in the white or the gray matter. Marked ballooning of the Betz cells also is in complete disagreement with the findings of Turnbull and McIntosh and of Perdrau. It could, perhaps, be considered that there was a causative relation between the brain pathology in this case and the spinal anesthesia, but the absence of spinal cord material does not permit any definite conclusion in that respect.

Case 2, which showed no myelin damage or extra-adventitial infiltrates, is readily differentiated from the postvaccination encephalitis. The case was not one of poliomyelitis, as there was no cellular damage in the medulla or spinal cord. No conclusion could be reached as to the etiology of encephalomyelitis in this case. No serological study was done.

Since Cases 1 and 2 were morphologically not those of postvaccination encephalitis, and since there was no encephalitis in Cases 3 and 4 (the patients died of acute hepatitis and acute focal myocarditis, respectively), one may state that none of the patients on whom a clinical diagnosis of postvaccination encephalitis was made in New York in 1947 died of that complication. Furthermore, the final figure on the number of diagnosed cases of postvaccination encephalitis must be reduced from 45 to 41.

The cases of the two infants, in whom encephalitis was an accidental microscopic finding, presented considerable diagnostic difficulties. In view of some features similar to the findings of Turnbull and McIntosh and other authors, these cases were diagnosed as possible instances of postvaccination encephalitis.

In Case 5, that of generalized vaccinia in a child with chronic eczema, the predominant

lesion was infiltration of the adventitia of numerous venules by large mononuclear cells. The lesions were most numerous in the region of the pons, as described by Turnbull and McIntosh, by Perdrau, and by Leifer [7] in postvaccination encephalitis. No myelin damage was found in the first few blocks. However, when numerous additional blocks of tissue were taken, a few areas of early degeneration of myelin, with beginning extra-adventitial cellular infiltration, were found in the corpus callosum (Fig. 5). The appearance of these areas bears a strong resemblance to the first illustration in the case of Hassin and Geiger [8] except for the caliber of the vein, which was greater in their illustration. In that case, a fully developed picture of postvaccination encephalitis, including perivascular demyelination, was found 31 hours after onset of the neurological manifestations. In our Case 5, a child with generalized vaccinia who was moribund showed a few neurological signs (nystagmus and spasticity of the extremities) only four hours before death, and probably died in an earlier stage of postvaccination encephalitis than any patient reported. This may explain the small number of areas of myelin damage with small extra-adventitial infiltrates in a case which otherwise showed the characteristic, predominantly pontine, distribution of venules with mononuclear adventitial infiltrates. It is of interest to note that, while the peripheral blood of the patient showed a marked leucocytosis (85% neutrophiles), the cells lined up against the endothelium in the lumen of the cerebral venules were almost exclusively large mononuclears, which in places seemed to be forcing their way into the walls of the venules with infiltrated adventitia.

Case 6 presented a difficult clinical problem because of pertussis, confirmed bacteriologically and hematologically, complicated by pneumonia. The child had a single episode of generalized twitchings 10 days before death; this was followed by coma and terminal hyperthermia. The neurological manifestations were attributed to pertussis encephalopathy. However, microscopic findings in the brain failed to show the changes observed in the encephalopathy of pertussis. There was no eosinophilic, anoxemic degeneration of the Purkinje cells of the cerebellum or of the pyramids of the hippocampus (Husler and Spatz [9]) and no lymphocytic plugs in the veins and capillaries (Dolgopol [10]), despite the high degree of peripheral lymphocytosis. Instead, several foci of residual disseminated encephalitis were found in the cortical white matter. In view of the recent vaccination campaign in the city, these findings suggested the possibility of a residual, mild postvaccination encephalitis. Since the chart of this patient showed no reference to vaccination, the family was contacted, and it was learned that the child had been vaccinated seven weeks prior to death and had developed pertussis about one week after vaccination, being treated at home for three weeks, until the onset of pneumonia. It became apparent that if a mild encephalitis developed some 10 to 15 days after vaccination, it occurred during the course of pertussis, obscuring the clinical picture. At the time of death, some five weeks later, the encephalitis was in the subacute stage, the stage of repair.

The subacute picture of postvaccination encephalitis was described in a case of Turnbull and McIntosh. The number of veins showing adventitial infiltrates was smaller than that in the acute stage. The infiltrating cells were large and small lymphocytes, plasmocytoid cells, and fibroblasts. Perivascular changes of the white matter consisted in early gliosis, with occasional fat-containing phagocytes between the glial cells. The case of Leifer [7] presented essentially similar changes. In our Case 6, the extra-adventitial changes consisted of eccentric collections of glial and mononuclear cells in the loose white matter. The adventitial infiltrates contained lymphocytes, some larger cells with dark cytoplasm, and a few phagocytes with foamy cytoplasm. The character of the lesions was similar to that described by Turnbull and McIntosh and by Leifer, but their number was smaller. The cases of those authors, however, presented a full-blown

clinical picture of the disease of the central nervous system, so that the number and size of the lesions could be expected to be greater than in our case, in which there was no clear-cut clinical encephalitis.

SUMMARY AND CONCLUSIONS

The actual incidence of postvaccination encephalitis is probably smaller than the number of cases diagnosed on a clinical basis. The clinical basis is, at present, the only method for diagnosing the disease. The original number of cases diagnosed as postvaccination encephalitis among some 5,000,000 vaccinated persons in New York City was 49, with 8 deaths. It had to be reduced to 45, after the gross necropsy findings proved that 4 patients had died of unrelated diseases of the central nervous system. Among the remaining four fatal cases, microscopic examination showed that two of the deaths were caused by acute hepatitis and by acute focal myocarditis, respectively, and that both had congestive encephalopathy. The remaining two cases showed encephalitis morphologically different from postvaccination encephalitis. With all fatal cases excluded on the basis of necropsy findings, the number of cases of clinical postvaccination encephalitis was reduced to 41.

On the other hand, encephalitis morphologically suggestive of postvaccination encephalitis was found on routine examination of the brains of two infants in cases which were not diagnosed clinically as that condition. In one case an infant with generalized vaccinia showed some neurological signs four hours before death. The involvement of the brain was extensive, although demyelination was in an incipient stage. Had the patient lived a few more hours, the clinical picture would probably have been more distinct and a clinical diagnosis of encephalitis might have been possible. The other infant, who developed pertussis one week after vaccination and died of pneumonia seven weeks after vaccination, showed some neurological manifestations which were attributed to pertussis encephalopathy. The brain showed disseminated healing foci of encephalitis suggestive of the subacute stage of postvaccination encephalitis.

With these clinically undiagnosed but morphologically probable cases included in the total, the incidence of postvaccination encephalitis among 5,000,000 persons vaccinated in New York City in 1947 was 43 cases, with 2 deaths.

Miss Gladys Haber prepared the histologic material. Mr. Edward Entin did the photographic work.

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EFFECT OF LARGACTIL (CHLORPROMAZINE) ON HUMAN SPASTICITY AND ELECTROMYOGRAM

Preliminary Report

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and
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THE PURPOSE of this paper is to present the electromyographic results of the intravenous administration of chlorpromazine (Largactil) to patients with spasticity due to an upper motor neuron lesion. Although only 13 patients have been studied to date, the results have been so dramatic that they deserve early reporting, especially since the effect of chlorpromazine on spasticity has not been described previously. Moreover, we have reason to believe that chlorpromazine may be effective in other motor disturbances (e. g., tremors) and so merits a wider trial outside its present restricted field of anesthesia and psychiatry. No attempt will be made here to review the rapidly expanding literature on chlorpromazine, nor will the chemistry be discussed. These matters are dealt with adequately in recent papers by Anton-Stephens [1]; Delay, Deniker, and Harl [4]; Lehmann and Hanrahan,[10] and Terzian.[14]

After the observation by one of us (A. S.) that a psychiatric patient with coincidental spasticity and paralysis due to an upper motor neuron lesion was relieved of the spasticity while on chlorpromazine therapy, we undertook an electromyographic study of a series of patients to evaluate the effects of the drug. This technique was employed because it provides a realistic permanent record of the presence or absence of activity in striated muscles and because it is less fallible than ordinary clinical observations. As early as 1940 Hoefer and Putnam * studied the action potentials in spastic conditions, and in 1952 Hoefer [6] reviewed the physiological mechanisms in spasticity as studied by electromyography.

In spasticity, one of the incapacitating features is the serious impairment of useful function, even though there has been considerable maintenance or recovery of voluntary movements. There is often so much activity in both antagonists and prime movers that the voluntary movements become a grim caricature of what the patient's brain has willed. Therefore, it is obvious that any treatment that can abolish or reduce spasticity in patients who have upper motor neuron lesions but who possess some residual power is of real usefulness. The economic and social factors involved are too apparent to discuss.

MATERIAL AND METHODS

Thirteen adult patients (9 men; 4 women) have been studied to date. All but one of these are inmates of Ontario Hospitals, and all have lesions of the upper motor neuron resulting in partial paralysis and disabling spasticity. Nine of the patients are old cases of hemiplegia due to cerebral vascular accident or cerebral inflammatory disease. Of the four remaining patients, the first has a high bilateral spinal cord lesion; the second has a bilateral lesion in the lower cervical region; the third has had most of one cerebral hemisphere removed because of severe trauma in an accident, and the last has had a temporal lobe removed because of brain abscess. An associated symptom in one female patient is a marked Parkinsonian tremor, about which we shall comment later.

Each patient has been under medical care for a number of years, and his or her physical condition has continued unchanged. It was a simple matter to reevaluate the neurological state.

The actual tests were performed in a more or less standard procedure, with modifications to meet

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* References 7 and 8.

special circumstances. After some experimentation we found that in all but two cases the best criterion of spasticity to record is the simplest of all stretch reflexes, the knee jerk. This reflex is generally considered to be a monosynaptic one, and, in any case, it does not normally involve a spread of excitation in the spinal cord. In one patient there were external factors that denied us the use of spasticity and compare it before with that after the administration of the drug in each patient individually.

A preliminary set of tests and recordings was made on each patient; 50 mg. of chlorpromazine was rapidly injected intravenously, and then repeated tests and recordings were made at frequent measured intervals of time.

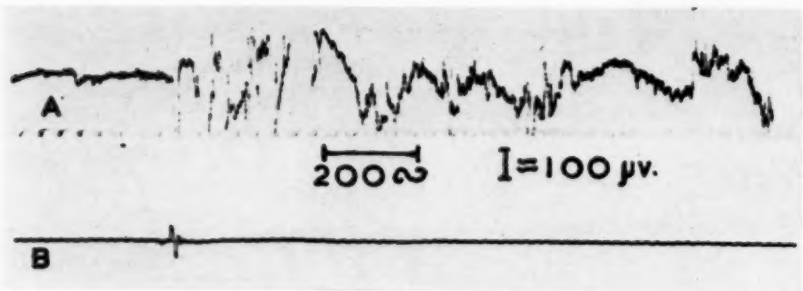

Fig. 1.—Electromyograms of the knee jerk in quadriceps femoris before (*A*) and three minutes after (*B*) the intravenous administration of chlorpromazine to a spastic patient. Record *A* shows a prolonged shower of action potentials lasting for more than a second; *B* shows a very brief normal burst.

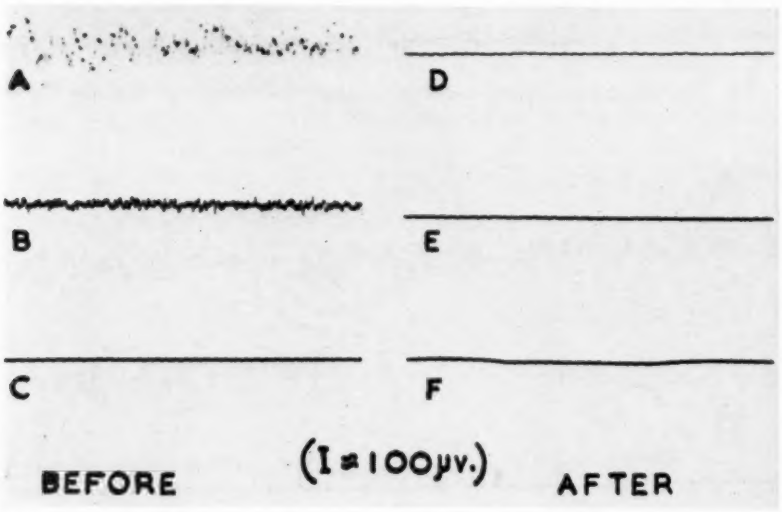

Fig. 2.—Effect of intravenous injection of chlorpromazine on various types of electromyographic activity in spastic patients "at rest." *A* (marked activity) and *B* (low-grade activity) become normal, i. e., have no activity (*D* and *E*, respectively). *C* (no activity) continues unchanged (*F*).

the knee jerk, and so we used the criterion of ankle clonism. In the remaining patient spasticity was not marked in the upper limb and was demonstrated electromyographically as a continuous high level of activity in the biceps brachii. The essential factor to be remembered is that we could evaluate one or another sign (or concomitant finding) of

The electromyographic technique employed has already been described elsewhere by Basmajian and Bentzon.[2] In brief, unipolar needle electrodes, as designed by Jasper,[9] were employed. In 11 cases (in which the knee jerk was to be recorded) the needle electrodes were placed in the quadriceps femoris. When ankle clonus was being observed,

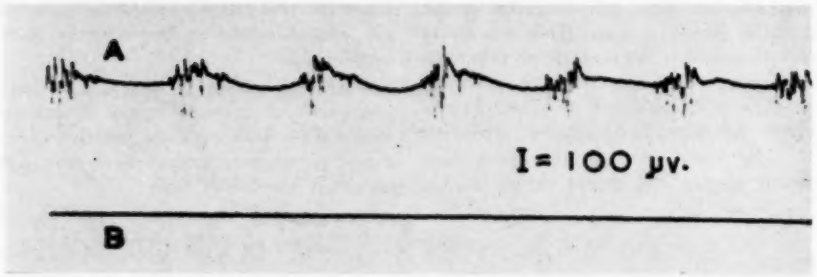

Fig. 3.—The "resting" electromyogram of a patient with Parkinsonian tremor, showing short bursts of potentials at intervals of one-fifth second (*A*), becomes normal (*B*) within three minutes of the injection of chlorpromazine.

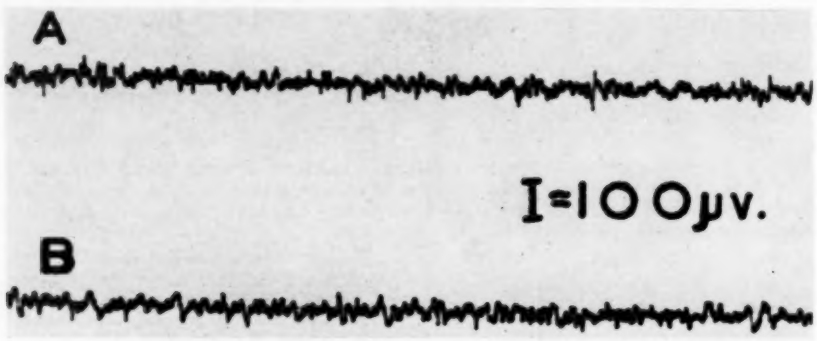

Fig. 4.—The electromyograms of a voluntary contraction in a spastic limb that has residual power before (*A*) and after (*B*) the injection of chlorpromazine are similar.

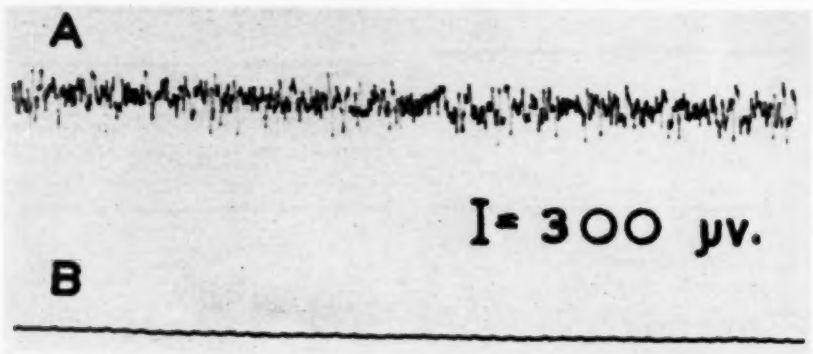

Fig. 5.—Irradiation of stimuli to quadriceps femoris resulting from a patient's squeezing an observer's hand with her own. Electromyogram *A*, before chlorpromazine, shows marked activity; *B*, three minutes after the injection, shows no activity.

the needle was placed in the calf, and in one subject action potentials from the biceps brachii were recorded. The myographs used were (1) a Philips, mark IV clinical electromyograph, and (2) a Stanley Cox special-design six-channel electromyograph. Both these are capable of extremely high gains with minimal distortion, and both include cathode-ray oscilloscopes for observation of potentials. The faces of the oscilloscopes are photographed on 35-mm. continuous-strip moving photographic paper or film.

During the myographic tests levels of consciousness were noted, and at other times parallel electroencephalographic and clinical observations were made.

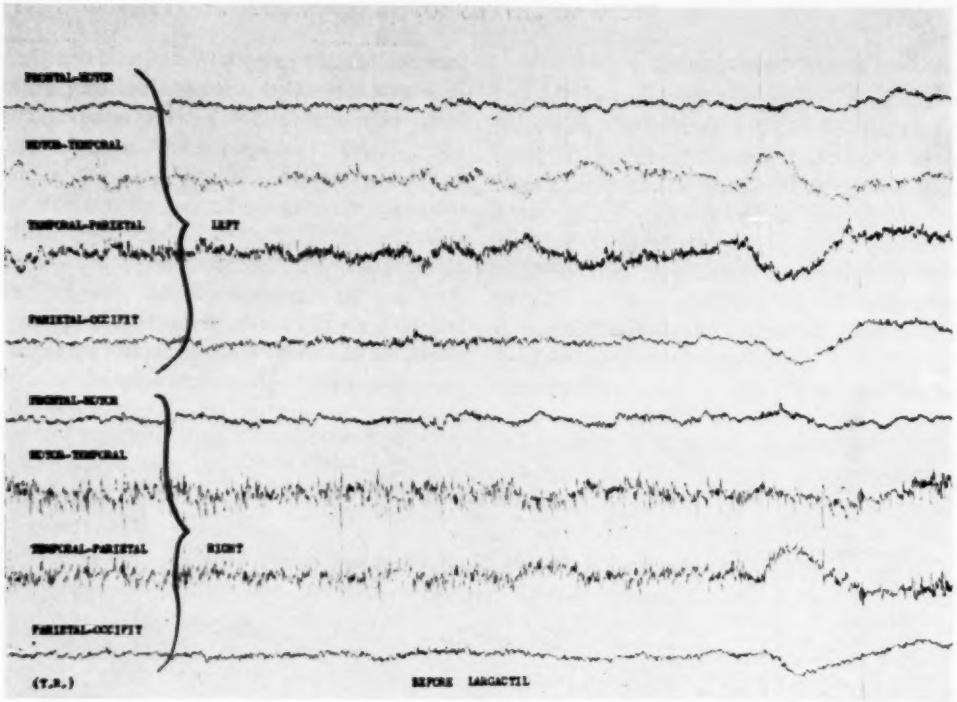

Fig. 6.—EEG of a patient with spasticity before receiving chlorpromazine, showing continuous "muscle artifacts," which mask cortical activity (patient markedly spastic).

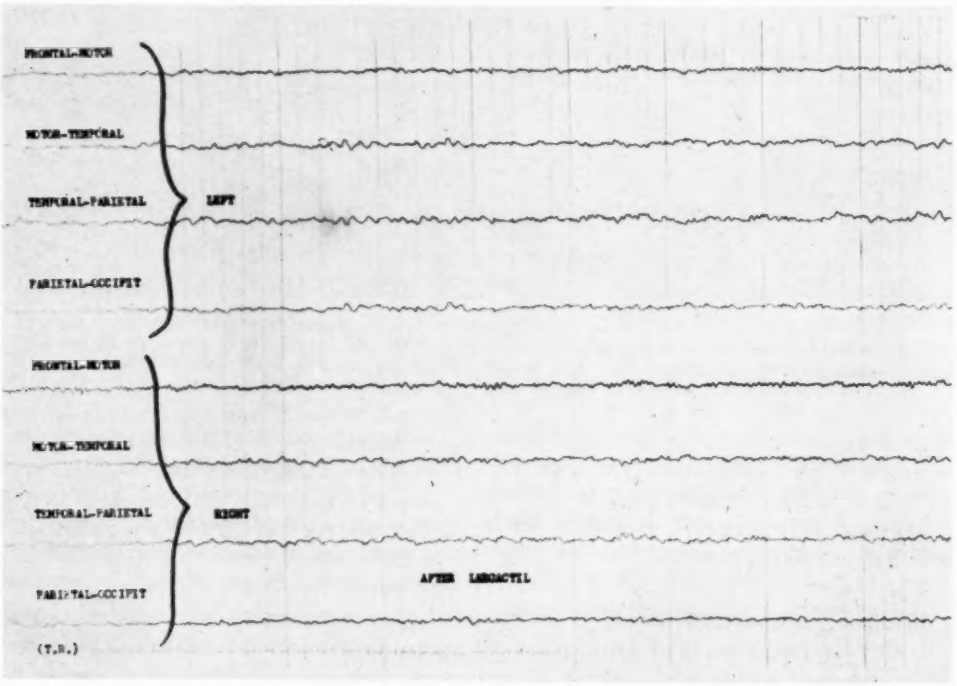

Fig. 7.—EEG of patient (same as in Figure 6) after receiving chlorpromazine, showing signs of mild drowsiness. (Patient now shows no signs of spasticity.)

OBSERVATIONS

Before receiving chlorpromazine, the patients all exhibited a marked spasticity on passive manipulation of the involved limbs. In 11 patients the knee jerk could be used as a criterion and was highly exaggerated clinically and myographically (Fig. 1, *A*). One patient showed continuous marked muscular activity at "complete rest" in spite of our efforts to induce maximum relaxation (Fig. 2, *A*). Five showed continuous "low-grade" activity (Fig. 2, *B*), and another showed rhythmic bursts of potentials characteristic of the Parkinsonian type of tremor (Fig. 3, *A*). The remainder could be relaxed completely (i. e., muscle potentials were absent), just as with normal persons (Fig. 2, *C*).

Within three minutes following the injection of chlorpromazine, 11 of the 13 patients (86%) showed a dramatic reduction of the spasticity and in them the electromyographic findings became essentially normal; the knee jerk now resembled that of a healthy person both clinically and electromyographically (Fig. 1, *B*). The six patients who showed marked or low-grade activity at "rest" before treatment now showed a normal absence of potentials (Fig. 2, *D* and *E*). The patient with a sustained Parkinsonian type of tremor now showed electromyographic "silence" at rest (Fig. 3, *B*) during the period of activity of chlorpromazine, which is about two hours when the drug is given intravenously.

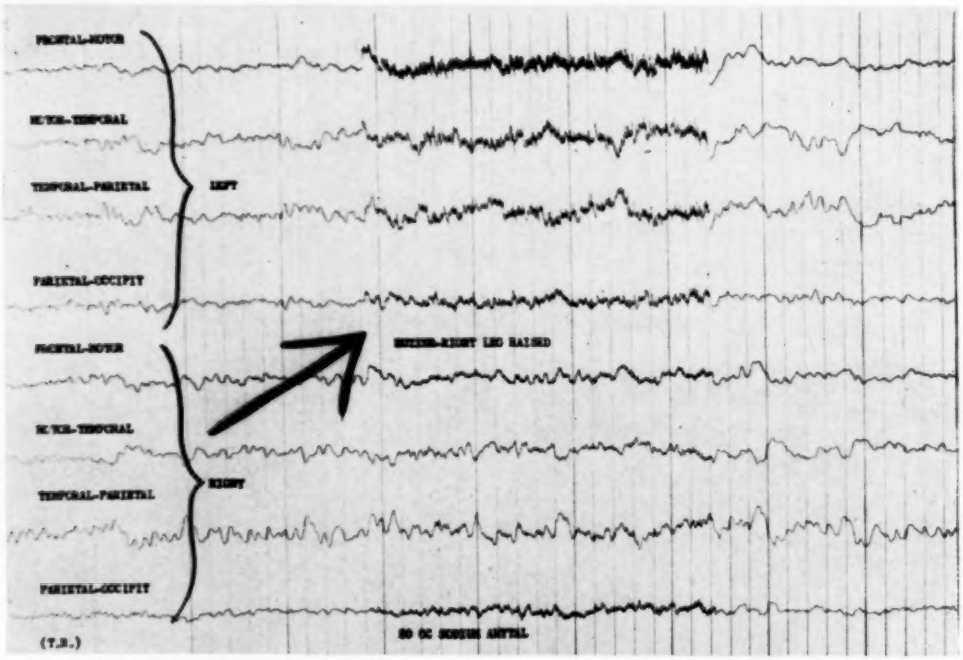

Fig. 8.—EEG of patient (same as in Figures 6 and 7) indicating moderate to deep sleep following intravenous injection of thiopental (Pentothal) sodium (1 gm.). Arrow is at point at which patient was aroused by a loud buzzer; he quickly went back to sleep. (Patient shows signs of spasticity in spite of deep sleep.)

Voluntary contractions were not affected clinically or myographically (Fig. 4).

In 2 of the 13 patients (14%) the results were not as marked; nevertheless, considerable improvement was demonstrable with our standard dose of 50 mg.

In five patients we made tests to study the spread or irradiation of stimuli in the spinal cord. This is a well-known phenomenon, which also occurs in strychnine poisoning

and in tetanus. It consists of a widespread motor activity ("mass response") following a localized stimulus. While recording from electrodes in the quadriceps, we asked the patient to cough or to squeeze the grasped hand of an observer; we tapped the midshaft of the tibia lightly with a reflex hammer or performed a "Babinski test." Before the administration of chlorpromazine the typical widespread response was obtained. Within three minutes after the injection of the drug irradiation was abolished (Fig. 5) in four of the five patients and was markedly reduced in the remaining one, this patient being one of the two whose knee jerk did not become completely normal.

Most of the patients were made drowsy by the intravenous dose but were nevertheless highly cooperative. In two instances sleepiness was fairly marked; in two others it was severe, although actual sleep was prevented by engaging them in conversation. This effect of chlorpromazine is now well known, and is perhaps its chief handicap.

Generally, all the effects of the intravenous injection lasted about two hours, with gradual reappearance of the symptoms.

Six of the patients were studied by means of an EEG as well, which showed that the reduction of spasticity was not related to a decrease of consciousness (Figs. 6 and 7). This finding is in contrast to the effect of barbiturates, which reduce spasticity only when they have produced deep coma (Fig. 8).

COMMENT

The dramatic reduction of spasticity by the intravenous injection of chlorpromazine suggests that the drug may find usefulness in a variety of situations. Because the drug may be given by mouth with similar, though less dramatic, results, it should be tried in maintenance doses in selected patients with lesions of the upper motor neuron. It is true that not enough experience has yet been accumulated in regard to the long-term effects of the drug, but it is hoped that the present report will stimulate adequate trials in a large number of patients.

Another useful field that suggests itself is in the retraining and rehabilitation of patients recovering from injuries and other lesions of the pyramidal pathway. In such circumstances the intravenous or intramuscular injection of the drug may help to solve for the physical therapist one of the ever-present problems in the retraining of the spastic paralyzed limb. The potential usefulness of chlorpromazine in cerebral palsy is an obvious application which we have just begun to investigate.

We have had no opportunity, as yet, to try chlorpromazine in other conditions in which spasticity or hypertonicity of one form or another may play a role, e. g., tetanus, Volkmann's ischemic contracture, Thomsen's disease (myotonia congenita), and overactivity of antagonists in lower motor neuron disease. Since chlorpromazine is contraindicated in the presence of infection, caution should be exercised in its possible use to reduce the painful spasticity of acute poliomyelitis.

Our incidental finding that tremor of the Parkinsonian type was abolished in one patient also merits further study. Of course, the effect on tremors of other types must be studied as well. Readers interested in the electromyography of tremors should consult the papers by Bishop, Clare, and Price [3]; by Hoefer and Putnam,† and by Lindsley, Schreiner, and Magoun.[11]

In most of our cases chlorpromazine made the stretch reflex normal and abolished spasticity of the involved limbs, without affecting volitional activity. The exact site of activity of the drug can only be guessed at. Judging by our finding that volitional activity is unaffected by the dosage employed, while keeping in mind that our present myographic technique will not reveal minor changes in individual motor-unit potentials, the site of activity probably is not "distal," i. e., at the myoneural junction. Nonetheless, we should not ignore the finding of Himwich [5] that promethazine (Phenergan), which is closely related chemically to chlorpromazine, has antiacetylcholine activity, both in vitro and

† References 7 and 8.

in vivo. Parker,‡ in a series of unpublished experiments on the isolated nerve-muscle preparation, found that chlorpromazine in high concentration (40 mg. per liter) depressed the preparation. It is very unlikely that such concentration of the drug is obtained in any part of the human being with a dose of 50 mg. intravenously. In general, then, Parker's findings appear to confirm our conclusion that in clinical doses the effect of the drug is not peripheral.

Judging by the clinical effects on psychotic and on hyperexcitable patients, chlorpromazine can be said to affect higher centers. However, the exact level of its action and its mode of action are unknown. Does it stimulate descending inhibitory impulses or repress facilitatory ones?

Two possible explanations have been offered for the pathological exaggeration of the myotatic reflexes following an upper motor neuron lesion. According to the first explanation, the spinal stretch reflex has an intrinsic capacity for exaggeration, and when deprived of the control of higher suppressor areas it increases itself. The second is that the increase of the reflexes is due to enhancement of the bulbar facilitatory systems, which are normally balanced by the inhibitory system of the midbrain. According to the recent investigations of Lindsley, Schreiner, and Magoun, the second explanation is likely to be the more acceptable.

The theoretical explanation of the mode of action of chlorpromazine in decreasing spasticity is very difficult. For this, further experimental studies, perhaps with stereotatic apparatus, would have to be carried out. A thorough research on its actions may actually help to clarify our concepts of the pathogenesis of spasticity (and/or hypertonicity) and of the mechanisms in the spinal cord and brain that have been disturbed by an upper motor neuron lesion.

In 1948, Szatmari and Mészaros reported a series of chronaximetric studies on the effect of caramiphen (Panparnit) in spasticity and rigidity. This drug has a chemical structure somewhat similar to that of chlorpromazine. It was found that rigidity is characterized by isochronism between a muscle and its antagonist, which, after administration of caramiphen, shifted to a physiological heterochronism parallel with the reduction of rigidity. After some theoretical consideration, it was suggested that caramiphen might act on the low midbrain reticular system in decreasing the tone of the facilitatory systems ("deprivation paralysis," Ward).

Clinically, chlorpromazine decreases anxiety and tension, and, in the EEG, it causes a mild progressive synchronization of the electrical pattern. The central activating system described by Magoun and his co-workers normally arouses and alerts the organism. On the one hand, it exerts an over-all effect on the consciousness, and, on the other, it exerts marked facilitatory influences downward, subserving behavior facilitation of the motor system. In spasticity it has been proved by Magoun that there is an imbalance between the facilitatory and the inhibitory systems of the midbrain characterized by increased facilitation and decreased inhibition. Thus, chlorpromazine, on acting on the central activating system upwardly, decreases tension of the cortex, and, acting downwardly, it decreases "tension of the muscles" and so decreases spasticity.

SUMMARY AND CONCLUSIONS

The effect of chlorpromazine (Largactil), which has been used in anesthesia and psychiatry as a depressant of increased psychomotor activity, is reported for the first time on patients who have upper motor neuron lesions and who exhibit disabling spasticity.

Given intravenously, 50 mg. of chlorpromazine produced immediate complete relief of spasticity (clinically and electromyographically) in 11 of 13 patients (86%) with marked, though incomplete, improvement in the remaining 2. The effects lasted about two hours and were not related to a decrease in consciousness as measured by the EEG. Chlorpromazine normalized the stretch reflex—exemplified by the knee jerk

‡ Parker, J. M.: Personal communication to the authors, 1954.

—and it abolished, or greatly modified, all the clinical and electromyographic signs of spasticity in most of the patients. This includes a decrease or abolition of the phenomenon of irradiation of stimuli.

Chlorpromazine did not affect the residual or recovered voluntary activity of muscles.

Further expanded studies are indicated. There are a number of diseases and conditions, e. g., cerebral palsies, tetanus, Volkmann's contracture, Thomsen's disease, and overactivity of antagonists in lower motor neuron lesions, in which it may also prove useful. Oral maintenance doses may be feasible in many patients, as it has been in psychiatry. In other cases, parenteral administration of the drug may allow more rapid retraining of spastic limbs.

The site of activity probably is not at the myoneural junction. Further studies may contribute to a better understanding of the underlying physiology of the neural pathways involved. Several possible modes of action have been discussed.

In one patient, Parkinsonian tremor was completely abolished during the period of activity of the drug. The effect of the drug on tremors of all types must be investigated.

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PHENOMENON OF RELIEF BY FLUSH IN MULTIPLE SCLEROSIS

Its Use As a Foundation for Therapy

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VARIOUS gross changes in the retinal blood vessels in cases of multiple sclerosis have been described in recent years. They are visible opthalmoscopically. So far, microscopic changes have not been described, nor has there been any recorded opportunity to look for them.

Rucker has reported "venous sheathings," which give the appearance of perivenous white, thickened tissue. His photographs suggest narrowing of the vessels at the sheathed areas.* Rucker did not study associated visual function or disturbance.

With Franklin, I have described narrowed areas in both retinal arterioles and venules (Fig. 1). There were associated visual defects; most of them were so located as to be explicable by the constrictions. Frequently, also, rapidly acting vasodilating drugs promptly reduced or abolished the visual disturbances, at least temporarily. The effect of these drugs upon the constricted areas of the vessels was less certain, although frequently Franklin thought he saw a widening; the vascular bed as a whole, however, was grossly widened by at least amyl nitrite.†

Most recently, Haarr has reported perivenous lesions which he describes as periphlebitis.[9] He, as well as Rucker, reported changes only in the venules.

Supported by the Fund for Research, Inc.

Mann Fine Chemicals, Inc., supplied the histamine phosphate (Mannistamine) used in this project.

From the Neurological Service of the Mount Sinai Hospital; Dr. Morris Bender, Chief Neurologist.

* References 1, 2, and 3.

† References 4 through 8.

In our previous reports, the constricted areas were designated as spasms. However, we have now seen that the constrictions may sometimes endure for many years, and it is possible that they represent an anatomical, rather than a physiological, change. Rucker, too, found that his sheathings persisted from a few months to two years, and in one case it was observed that over a period of nearly five years no change occurred.[3] Yet in at least a few instances we have seen constrictions of very brief duration, and these would indeed seem to be spasms; they could, of course, themselves be the result of anatomical changes, such as those just postulated.

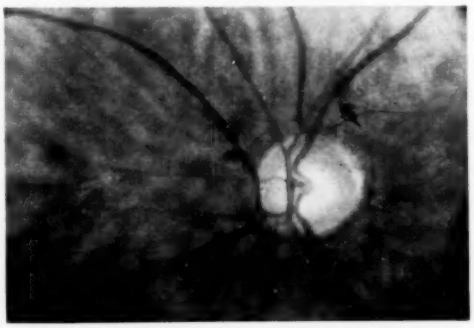

Fig. 1.—Constriction in a retinal venule. It remained unchanged over a two-year observation period.

It would seem probable that all the authors are alluding to the same lesion, at least as far as the venules are concerned.

The evidence at hand does not touch upon the cause of the constrictions. The search for this is an additional problem.

PHENOMENON OF RELIEF BY FLUSH

Once it was established that visual disturbances were often associated with the constrictions, the effect of rapidly acting

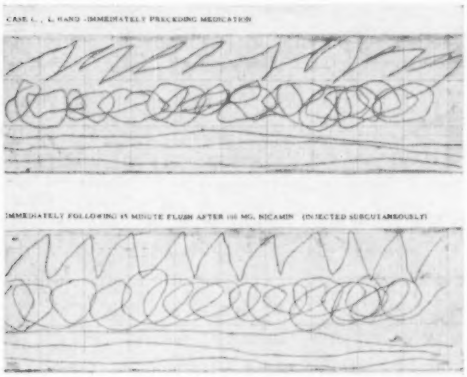

Fig. 2.—Ataxia of the upper extremity of recent onset. Line drawing made a few minutes before and after a flush.

vasodilating drugs upon these disturbances was studied, as indicated above.‡ The alleviation of the disturbance by such drugs is "relief by flush."

In subsequent studies, I found that vasodilating drugs produced prompt reduction or abolition of any symptomatic phenomena of multiple sclerosis, and not merely of visual ones§ (Figs. 2 and 3). The existence of this phenomenon has been confirmed by several workers.‖ Twenty-one cases were studied with Dr. Paul Draper, in Colorado Springs, also.

TABLE 1.—*Demonstrations of Relief by Flush*

	No. of Cases	No. of Symptomatic Phenomena	Source
Positive			
Old.....	37	145	Brickner and Franklin *
New.....	49	119	Current series †
Totals.....	86	264	
Failures	10	12	Current series (see Table 3)
Too long duration.....	10	27	Current series
Could not be evaluated.....	6	12	Current series (psychological factors)

* References 5 through 8.
† From here down some of the cases overlap.

‡ References 4 and 5.

§ References 6, 7, and 8.

‖ References 10 through 13. Schmid, E. E.: Personal communication to the author. Bell, E., Jr.: Personal communication to the author.

PRESENT INVESTIGATION

Statistical Summary of Demonstrations of the Phenomenon.—By now the phenomenon of relief by flush has been demonstrated often (Table 1).

Table 2 summarizes the results of the present series in 69 cases, with 313 symptomatic phenomena exclusive of 6 cases which could not be evaluated because of psychological factors.

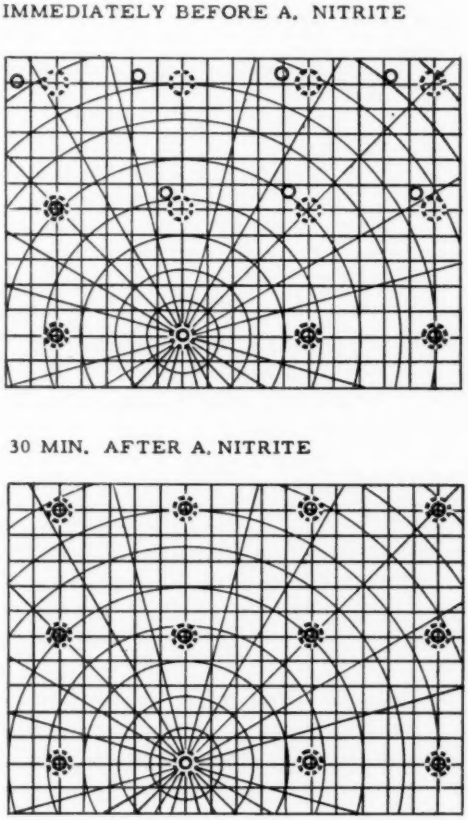

Fig. 3.—Diplopia of recent onset just a few minutes before and after a flush.

TABLE 2.—*Relief by Flush Related to Duration of Symptomatic Phenomena*

No. of Symptomatic Phenomena	Duration of Symptomatic Phenomena Before Treatment	Positive Response		No Response	
		No.	%	No.	%
7	Some hours	6	85	1	15
6	D. T. P.*	3	50	3	50
13	Days	10	77	3	23
8	1 wk.	7	87	1	13
26	10 days-6 wk.	25	97	1	3
28	2-10 mo.	28	100	0	0
12	Recent †	11	91	3	9
13	1-2 yr.	8‡	61	6	39
21	2 yr. and more	0	0	21	100
28	Unknown	21	75	7	25
Totals		119		46	

* Appeared during treatment period.

† "Recent" means that the exact time of onset is unknown but was within a few weeks of treatment, or that the symptomatic phenomenon was a continuously progressive one.

‡ Of these eight instances, relief by flush was demonstrated solely in relation to spasticity in seven.

As Table 2 shows, relief by flush may be expected to appear with symptomatic phenomena of up to about 10 months' duration, according to the present data. Symptomatic phenomena of a year's duration or more do not ordinarily show the relief, except sometimes for spasticity. In one case, however, ataxia said to be of a year's duration showed relief; this result is so deviant from all the others as to raise doubts concerning the accuracy of the history.

Instances in which relief by flush failed to occur without known reason are summarized in Table 3.

Promptness of the Effect.—The relief occurs within 20 to 50 or 60 minutes. The immediate, often slightly shocking, effects of the flush must be recovered from before the neural relief becomes manifest.

Relation of Effect to Duration of Symptomatic Phenomena.—Symptomatic disturbances of extremely recent origin (six weeks or less in duration according to present data) may disappear after a single flush, and not return. Older disturbances often return in three to four hours; relief can promptly be obtained again by repeating the flush at the indicated time.

Scars are, of course, not influenced; the effect could be expected only if lesions, or parts of lesions, are not yet scarred.

Controls with Other Chemicals.—Control studies employing inert chemicals could not be adequately designed. Except when CO_2 (5% in 95% oxygen) is used, patients are keenly aware of the flush, and there is no certainty about the lack of vasodilating properties of safe, inert gases.

Relation of Phenomenon to Pathogenesis of Lesions.—It is thought that symptomatic phenomena are reversible under the following conditions: The neural tissue may still be viable but may function poorly because of reduced blood supply. Sometimes, especially with older lesions, there may be a central irreversible component, evidently surrounded by a reversible one; the amount of symptomatic disability is reduced by flushing, but a fixed core remains. This was first shown by the repeated reduction in size of a scotoma by flushes, with a permanent residual central scotoma.[5] Tissue death may, of course, result from too great or too prolonged a reduction in blood flow, possibly associated with thrombosis in some instances. In this way, the thromboses of Putnam and their role could be explained. ¶

It is postulated that at least one factor in the production of the neural lesions is deficient oxygenation, resulting from the con-

TABLE 3.—*Relief by Flush Not Shown, with Symptomatic Phenomena of Short Duration* *

Case No.	Patient	Duration	Comment
1	H. B.	D. T. P.†	Subjective sensation
2	S. B.	D. T. P.†	Subjective sensation
3	R. F.	D. T. P.†	Subjective sensation
4‡	S. W.	1 wk.	Very few trials (subjective sensation)
5	J. L.	5 days	Scotoma
6	G. S.	5 days	Scotoma
	G. S.	2 wk.	Field defect
7‡	L. K.	4 days	Careless self-treatment (blurred vision)
8‡	R. Z.	1 hr.	May have been there before (nystagmus)
9	M. W.	Gradual	Paresis of 1 leg
	M. W.	Recent	Paresis of 1 foot
10	H. F.	Recent	Paresis of 1 leg

* All these symptomatic phenomena ultimately remitted, except that in Case 8 (R. Z.).

† Appeared during treatment period.

‡ These cases are recorded as not showing the phenomenon, although there is doubt.

¶ References 14 and 15.

strictions. These may cause a direct reduction in blood flow, or may block the entrance or exit of a vascular branch, or may merely interfere with the speed and rhythm of blood delivery.

The relief of symptomatic phenomena is not considered "symptomatic relief." On the contrary, it is thought to bespeak a specific, basic factor in the pathogenesis of the neural lesions. Seen in the light of these observations and theories, the processes underlying the pathogenesis of the lesions in multiple sclerosis have something in common with coronary artery disease, in which either closure, or angina pectoris with little or no tissue damage may occur.

Relation to Other Studies in Which Vasodilating Drugs Are Used.—These studies are of a basically different nature from studies employing chemicals (which are also vasodilators) to treat supposed allergy in multiple sclerosis. Moreover, this procedure is not of the same order as any routine administration of a vasodilating drug without observation of the effect of each treatment on specific symptomatic phenomena. In routine administration of vasodilating drugs with periodic reports or examinations of the total condition, many of the specific effects of flushes are likely to be missed. A vasodilating drug should not be employed unless there is ample time to make the type of immediate follow-up study described here.

Controlling Spontaneous Remissions.—The characteristic occurrence of spontaneous remissions in multiple sclerosis has bedeviled all studies of the effect of treatment on the clinical phenomena. Ordinarily, studies of therapy take several years, and statistical evaluations must be attempted if any effort is to be made to control this factor. Even then, errors of interpretation may occur.

The problem of spontaneous remissions appears adequately controlled in the present studies. Here we are not concerned with the long-term effect of a therapeutic measure on the total condition of a group of patients. Instead, we are dealing with the case-by-case, almost immediate, effect of a procedure upon a specific symptomatic phenomenon.

Spontaneous or coincidental remissions would seem to be excluded by the following factors:

A. The regular occurrence of the relief within an almost uniform number of minutes.

B. The fact that the induction of relief can be repeated regularly if the symptomatic phenomenon returns.

C. The fact that relief, and the timing of relief, are regularly predictable under two conditions: (*a*) if the symptomatic phenomenon returns in a few hours after having been relieved once, and (*b*) in most previously untreated patients, with symptomatic phenomena not very old.

D. The fact that the phenomenon of relief by flush has been demonstrated at least 264 times in 86 patients. Failure to demonstrate the phenomenon when it could have been expected has been definitely seen with only 12 symptomatic phenomena in perhaps 10, but certainly 7, cases.

Psychological Factors.—The possibility that the relief obtained by flushing may be psychogenic is considered ruled out by points A to D (above), as well as by the total therapeutic scores (below). Even so, psychological effects may still occur and be impossible to diagnose with assurance, in individual cases. Some of the disabilities of the disease may be accentuated by psychological factors. Treatment, also, may have psychological effects which may either accentuate or reduce disabilities.

The correct evaluation of all these factors in each case is virtually impossible, under the essential conditions of treatment. It was considered that in all patients there are at least some psychological factors which influence the course of events to some degree, but that these were usually outweighed by factors A to D (above). Also, in a fairly large-sized group of patients, the psychological factors directing patients toward and away from therapeutic success might well balance each other. In view of the total

therapeutic scores (below), it was also thought that if the main effects of treatment were psychological, their number, predictability, and regularity of occurrence would require us to consider as psychogenic most of those disabilities in multiple sclerosis which are not yet irreversible, and this would be absurd.

Six patients in the series were indeed so conspicuously hysterical that it was deemed impossible to evaluate their therapeutic results at all.

Effects of Practicing Tests and of Resting.—These factors may lead to transient improvement in performing tests. They need to be controlled in any such study as this. In this series of cases they have been adequately controlled.

THERAPY FOUNDED UPON PHENOMENON OF RELIEF BY FLUSH

It has now become possible to deal with the phenomenon of relief by flush in such a way as to build a reliable therapeutic program upon it. It has already been said that symptomatic phenomena which are sufficiently new can usually be relieved or abolished; if the symptomatic phenomena tend to return, repetitions of treatment can be so planned as to keep them at a low level or nonexistent most of the time.

The original translation of the relief by flush phenomenon into a practical therapeutic program depended upon several points:

A. Ascertaining how long the beneficial effects of a single flush endured. It was found that some symptomatic phenomena of very recent onset disappeared after a single vasodilatation, and either did not return at all or returned only once or twice. Older symptomatic phenomena have a much greater tendency to return and need more systematic, persistent treatment.

B. Ascertaining whether a very sharply acting drug (amyl nitrite) or a more gradually and mildly acting one, like CO_2, is the drug of choice.

Sometimes symptomatic phenomena are transiently increased, rather than decreased, during the peak of the flush, and even for some minutes afterward. This seems to occur more frequently when amyl nitrite is used than when more mildly acting chemicals are employed.

Patients without marked general damage to the spinal cord can tolerate drastically acting chemicals better than those with it. This may be due to impairment of the blood pressure-regulating mechanisms in the spinal cord, in advanced cases.

C. Determining correct dosages.

D. The case-by-case, total working out of detailed means of prolonging or repeating the favorable results of individual flushes.

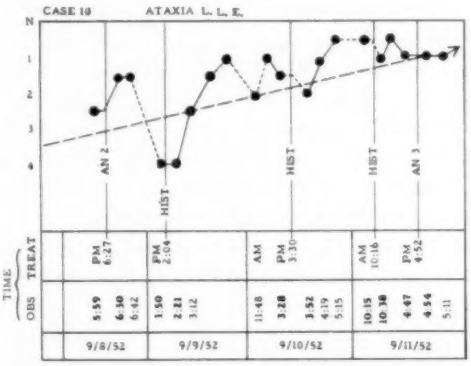

Fig. 4 (Case 10).—Line with dotted portions: Improvement of recurrent ataxia of left lower extremity of three months' duration (heel-knee test). Treatment had to be continued at least two or three times a week because the improvement lasted at most three days, and sometimes less. The improvement in the heel-knee test was markedly reflected in the gait. Histamine phosphate, U. S. P., 1%, was the drug of choice. The short broken lines indicate periods of hours without tests.

Line of dashes: Improvement in a recurrent diplopia. The diplopia did not improve with each treatment; it had a spontaneous remission.

The diplopia was of only six weeks' duration.

The Drugs and Their Usage.—The drugs used have been amyl nitrite (1 to 6 whiffs); CO_2 (5% and 10% in oxygen with rebreathing, the usual dose being 3 liters per minute for 10 minutes), and histamine phosphate U. S. P., 1%, given by iontophoresis at 5 ma. until a flush of the desired intensity is achieved. Occasionally, nicotinic acid has been employed, and rarely papaverine hydrochloride, given by vein. Also,

rarely, histamine phosphate U. S. P. has been given by intravenous drip, in an effort to prolong a too short and diminishing period of relief.

In some cases, one symptomatic phenomenon responds to one drug, but another drug is needed for others (Fig. 5). Such points as this illustrate the need for continued careful watching, in day-by-day treatment. At times a given dose of a drug seems to lose its effect, and either the dosage or the drug must be changed.

Occasionally, in cases requiring repeated treatment, almost every treatment is effective but an occasional one is not (Fig. 5). This may be because the flush never occurred at all (owing to a leak around an inhalation mask or other causes) or for unknown reasons. It is always well to make sure the flush occurs and to estimate its intensity.

Patients should lie prone until sometime after the flush is over. The time necessary for this varies with circumstances; 20 minutes has arbitrarily been used as a minimum. Dr. James Beazell, of Colorado Springs, has suggested elevation of the lower extremities, in addition.

Self-treatment at home, by the patient, can be an indispensable adjunct. However, continued, regular supervision is essential.

Patients should be trained in the evaluation of simple neurological tests, such as the finger-to-nose test. They should also be thoroughly instructed in all the principles underlying treatment; only with that background can they be prepared to be treated immediately if new developments occur, and only in that way can they understand the irreversibility of an old, scarred lesion, as contrasted with the probable reversibility of a fresh one.

Advanced Cases.—In advanced cases, the treatment of new symptomatic phenomena carries with it special difficulties. The drugs

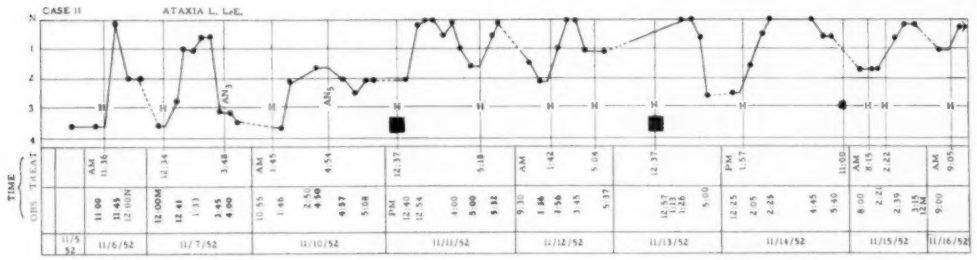

Fig. 5 (Case 11).—Ataxia of the left lower extremity of recent origin.

General Meaning of Curve.—Repeated treatments were needed for more than nine days because the improvement after each flush was not sustained. Gradually the post-treatment regressions became slighter in degree, until they almost faded out. Not shown is the continuation of treatments for a short time, with continued specific effect of each one, until normality was reached and sustained.

Difference in Effects of Different Drugs.—Amyl nitrite (3 to 5 whiffs) failed to produce relief by flush with this symptomatic phenomenon, while histamine phosphate (*H*), 1%, did produce it; the histamine phosphate administrations could then be used therapeutically. Amyl nitrite did affect other symptomatic phenomena.

Imperfections in Technique.—The broken lines indicate long periods in which no tests were made. The two places indicated by solid squares illustrate what the patient reported as happening at night when her symptoms became worse and she gave herself treatments; she failed to assess the intensity of the symptom a few minutes before treatment so that a grade could be given, and hence these particular observations as reported could not be used as first-class evidence of the effect of the particular flush involved. In two other places on the curve (second and seventh broken lines), the interval between our own pretreatment and post-treatment observations was unavoidably longer than an hour, and the value of these flushes as evidence is also reduced. These observations are included in Figure 5, to show what ones can and what ones cannot be properly employed in evaluation.

In the time recordings for 11/10 52, *2.50* appears slightly too far to the right.

themselves are more difficult to use safely. Old scars, with symptomatic results previously compensated for, may newly and irreversibly contribute to a disability, when associated with a new lesion.

Fulminating Attacks.—One fulminating acute attack of multiple sclerosis has been seen in which the phenomenon of relief by flush was repeatedly achieved, but the duration of relief did not exceed 10 minutes (histamine phosphate U. S. P. was given by intravenous drip). Gradually the interval shortened to zero. Perhaps an anticoagulant would have made a difference, but it was not given.

In two cases a fulminating attack occurred a day after long-continued daily treatment was stopped.

Means of Evaluating the Phenomenon and Its Therapeutic Use.—The means of evaluating treatment by observing the immediacy of the effect of flushes upon fairly new symptomatic phenomena are illustrated in Figures 4 and 5. In Figure 5 are two places indicated by black squares illustrating what the patient reported as happening at night, when her symptoms became worse and she treated herself; she failed to assess the intensity of the symptom a few minutes before treatment so that a grade could be given, and hence these particular observations, as reported, could not be used as first-class evidence of the effect of the particular flush involved. In other places on the curve (the second and seventh broken lines), the interval between our own pre-treatment and post-treatment observations was unavoidably longer than an hour, and the value of these individual flushes as evidence is also reduced. These observations are included in Figure 5 to show what ones can and what ones cannot properly be employed in evaluation. These standards are needed in order that one may avoid the intrusion of the problem of spontaneous remissions.

Figure 5 also includes some occasions on which one chemical (amyl nitrite) was ineffective, while another (histamine phosphate) was effective, in producing relief by flush.

Total Effectiveness of Therapeutic Use of Relief by Flush.—Table 2 shows that a high percentage (average, 90%) of symptomatic phenomena of not more than 10 months' duration, show the phenomenon of relief by flush. (Unexplained is the fact that only 50% of six symptomatic phenomena coming on during the treatment period showed relief by flush.) Analysis of the results by simple scoring seems to show no difference in response among symptomatic phenomena of various durations, provided they are of not more than 10 months' duration.

However, there is a marked difference between very new and older symptomatic phenomena in the way in which the effect of treatment is sustained. The newer the symptomatic phenomenon, the greater is the likelihood that the response to the flush will be sustained. The therapeutic results were sustained with about 90% of the symptomatic phenomena of not more than 6 weeks' duration.

Symptomatic phenomena of about six weeks' duration or less usually reached and maintained a fixed level of improvement after a few treatments. In those instances no more treatment was needed unless a new attack occurred. Symptomatic phenomena of more than six weeks' duration usually failed to maintain their level of improvement; they continually recurred and required long-continued (carefully timed) treatment in order to make use of the benefits they did derive from each treatment.

No patient who persisted in treatment was worse than before treatment except one of those listed in Table 3.

Six symptomatic phenomena in three patients have been treated within one hour of onset and five have responded promptly to the flush; the other may have responded but there is some doubt (Table 3, Case 8, [R. Z.]).

SUMMARY

A. Phenomenon of Relief by Flush.—Previously, constrictions and other gross

changes in retinal blood vessels have been described in multiple sclerosis. No report covering the histology of these vessels has yet appeared.

Visual symptoms evidently associated with these constrictions have been promptly reduced or abolished with rapidly acting vasodilating drugs. Later studies have showed that all types of symptoms could be similarly affected. This phenomenon is termed "relief by flush."

The phenomenon of relief by flush has now been demonstrated with 264 symptomatic phenomena, in 86 patients.

The phenomenon of relief by flush occurs within a few minutes of recovery from the flush.

Spontaneous, accidental, or coincidental remissions would seem to be excluded by the following factors:

A. The regular recurrence of the relief within an almost uniform number of minutes.

B. The fact that the induction of relief can be repeated regularly if the symptomatic phenomenon returns.

C. The fact that relief, and the timing of relief, are regularly predictable under two conditions: (*a*) if the symptomatic phenomenon returns in a few hours after having been relieved once; and (*b*) in most previously untreated patients, with symptomatic phenomena not very old.

D. The large number of successful demonstrations of relief by flush.

Psychological effects and practice effects are also considered excluded.

It is believed the phenomenon of relief by flush is not merely a symptomatic effect, but represents a specific factor in the pathogenesis of the lesions.

Ninety per cent of symptomatic phenomena of not more than 10 months' duration show the phenomena of relief by flush. (Unexplained is the fact that only 50% of six symptomatic phenomena coming on during the treatment period showed relief by flush.)

B. Use of Relief by Flush as a Foundation for Therapy.—The phenomenon of relief by flush has been employed as a foundation for therapy.

With careful timing of repetitions of treatment when necessary, a successful therapeutic program can be maintained in which the problem of spontaneous remissions does not seem to come up.

Analysis of the results by simple scoring seems to show no difference in response among symptomatic phenomena of various durations, provided they are of not more than 10 months' duration. However, the newer the symptomatic phenomenon, the greater is the likelihood that the response to the flush will be sustained. The therapeutic results were sustained with about 90% of the symptomatic phenomena of not more than six weeks' duration. Symptomatic phenomena of about six weeks' duration or less usually reached and maintained a fixed level of improvement after a few treatments. In those instances no more treatment was needed unless a new attack occurred. Symptomatic phenomena of more than six weeks' duration usually failed to maintain their level of improvement; they continually slipped back and required long-continued (carefully timed) treatment in order to make use of the benefits they did derive from each treatment.

No patient who persisted in treatment is worse than before treatment, except one of those listed in Table 3.

This procedure differs entirely from other uses of vasodilating drugs in multiple sclerosis.

In order to employ this procedure, two separate steps must be taken:

A. Demonstration of the phenomenon of relief by flush must first be attempted.

B. If the phenomenon can be demonstrated for certain symptomatic phenomena, study is needed to show how it can be used for the benefit of that individual patient. Techniques for doing this are described.

Miss Gertrude Clark and Mr. Warren Homer assisted in collating the data.

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EXTRACELLULAR SPACE IN THE CENTRAL NERVOUS SYSTEM

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A KNOWLEDGE of the volume and composition of the extracellular space in brain substance is of considerable importance in any investigation dealing with electrolyte concentrations in nerve tissue and with mechanisms of fluid shifts in cerebral edema. Although fluid partitions have been thoroughly studied in the body as a whole, and in muscle tissue in particular, there have been no well-established determinations of extracellular *versus* intracellular compartments in the brain.

One approach to the problem has been the use of chloride and sodium spaces. In such methods the two ions are assumed to be distributed completely in the extracellular phase; consequently, the content of chloride (or sodium) in cerebral tissue divided by its concentration in extracellular fluid results in a figure which may be called the chloride (or sodium) space. One immediate difficulty arises at this point in regard to the ionic concentration which one selects as comparable to that of extracellular fluid. Is it equivalent to that of serum ultrafiltrate or, more likely, to that of cerebrospinal fluid? Manery and co-workers, utilizing the electrolyte concentration of serum as the divisor, obtain the figures of 30% to 35% for both sodium and chloride spaces in small mammals.* Similarly, Elliott and Jasper [3] report a figure of 40% for chloride space in rabbits. These values seem quite high when compared with figures obtained by different methods and for other tissues, such as about 20% for total extracellular fluid in dogs [4] and about 10% for skeletal muscle in man.[5] Moreover, the basic tenets of this method are in doubt, for there is good reason to believe that both chloride and sodium exist in part as intracellular ions in nerve tissue.[6]

Another general technique which has been tried involves the intravenous infusion of a foreign substance which equilibrates rapidly between blood and interstitial fluids but will not penetrate into cells. It is then possible to measure extracellular volume either for total body or, by using tissue samples, for specific organs. Inulin, with its high molecular weight, lipid insolubility, lack of toxicity, and low osmotic capacity, has been most successfully used for this method.† Other substances which have compared favorably with inulin include ferrocyanide,[8] radioactive sulfate,[9] and thiosulfate.[10] Unfortunately, any application of such a technique to brain is complicated by the factor of the blood-brain barrier, which effectively resists penetration of each of these components into brain and cerebrospinal fluid.

In attempting to surmount some of these various difficulties, it was decided to try an in vitro diffusion technique similar to that used by Boyle and co-workers [11] for estimating interstitial space in frog sartorius. Slices of rat brain were incubated at 38 C in phosphate Ringer solution exposed to 100% oxygen for periods of time ranging from five minutes to three hours. The substances to be tested were added as isotonic solutions to the incubation medium and, after allowance for diffusion and equilibration, concentration of test substance was determined in both tissue slices and external medium. The space of diffusion could then be calculated. With such a method, the problem of the blood-brain barrier could be circumvented. Furthermore, after equilibration one could be sure that the composition of external medium was

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* References 1 and 2.

† References 4, 5, and 7.

identical with that of fluid occupying the interstitial compartment. The compounds selected for diffusion were inulin, because of its well-documented value for use in other tissues, and sodium ferrocyanide, because of the previous demonstration by Weed [12] that it will not penetrate the living cells of the nerve tissue.

METHODS

Incubation Chamber.—Since the experimental methods developed required a larger quantity of fluid medium and tissue slices than could be accommodated by the flasks of a Warburg apparatus, it was decided to use incubation chambers similar to those described by Boyle and co-workers.[11] In essence, these consisted of Pyrex test tubes of 32 by 200 mm., into the ends of which had been fused pieces of glass tubing with a capillary bore measuring 0.5 mm. The external ends of the tubing were connected by rubber tubing to a source of oxygen. Each chamber was fitted with a cork containing an 8 cm. length of glass tubing, which served as an air condenser to prevent excessive evaporation of the medium to be contained within. A bank of chambers was then fitted into a constant temperature bath set at 38 C.

The incubation medium consisted of appropriate quantities of phosphate Ringer solution, an isotonic solution of the substance to be diffused, 0.3 M dextrose, and 0.2 M sodium l-glutamate. The solutions were adjusted to pH 7.4 in all cases. The following is the formula used for ferrocyanide space experiments:

Phosphate Ringer solution	26.33 ml.
Sodium ferrocyanide 2.9 gm. per 100 cc.	10.0
Dextrose 0.3 M.	2.67
l-Glutamate 0.2 M.	1.0

In preparing the medium for insulin diffusion, because of its low osmotic capacity Pfanstiehl inulin was dissolved directly in phosphate Ringer solution in the proportion of 225 mg. to 75 ml. The complete formula was as follows:

Ringer-inulin solution	75.0 ml.
Dextrose 0.3 M.	5.34
l-Glutamate 0.2 M.	2.0

Incubation Procedure.—Brains obtained from adult male white rats were used in all experiments. The animal was etherized and quickly decapitated, and the brain removed. Slices were made freehand, and it was possible to obtain fairly uniform specimens of 1.0 mm. thickness, weighing about 100 mg. Thinner slices were not practicable because of a tendency to fragmentation while in the incubating medium. All slices were taken in a sagittal plane and from approximately the same region of the hemisphere in each case so as to maintain a reasonable uniformity in proportion of cortex, white matter, and basal ganglia. A group of two to three slices were weighed in a weighing bottle containing a known amount of Ringer solution and then transferred to the waiting incubation chamber. The procedure from decapitation to immersion of slices in the medium required 9 to 10 minutes. During incubation the slices were kept in motion by a fine stream of oxygen bubbles. Upon the conclusion of the incubation-diffusion process, the group of slices were washed in a beaker of Ringer solution for 10 seconds, then placed on a glass grill and dried with sharp points of filter paper as quickly as possible. They were then reweighed and retained for analysis.

Finally, in order to detect any remaining increment in weight or diffusing substance due to adherent medium, a group of control slices were dipped into a solution identical with the incubation medium for 10 seconds, were transferred to plain Ringer solution for 10 seconds, and then were dried in the same manner as the experimnetal tissue.

In the experiments in which chloride analyses were performed, isotonic dextrose was substituted for the Ringer solution in the 10-second washing procedure.

Chemical Analysis.—In each experiment analyses for the diffusing substance were carried out upon tissue slices in duplicate, control slices, samples of medium, as well as appropriate blanks and standards. In the analysis for ferrocyanide, each group of experimental slices was minced finely and extracted in distilled water added to a total volume of 20 ml. Control slices, because of their lower ferrocyanide content, were extracted in a total volume of 5.0 ml. The suspensions were then centrifuged at 2,500 rpm for 15 minutes and the supernatant used for ferrocyanide determination by the method of Husson.[13] The technique used for insulin analyses was that developed by Ross and Mokotoff [14] for tissues. Chloride was determined by the method of Sunderman and Williams.[15] Water content was found by drying minced tissue in a weighing bottle at 95 C to constant weight (24 to 48 hours).

Calculations.—Swelling of tissue slices was expressed as increment of weight in percentage of the original weight. From this gross figure was deducted the increment of control slices, representing the gain due to adherent medium. With practice in the technique, this latter figure became surprisingly constant, ranging between 3% and 4%.

Ferrocyanide or inulin content of tissues was expressed as milligrams per gram of wet tissue. The content in control slices due to adherent medium was substracted from the gross value. This, too, was found to be a relatively constant figure of low order. Ferrocyanide (or inulin) space was calcu-

lated as milliliters per 100 gm. of tissue by the following formula:

$$\text{Ferrocyanide space ml./100 gm.} = \frac{\text{ferrocyanide in tissue mg./gm.}}{\text{ferrocyanide in medium mg./ml.}} \times 100$$

Histological Technique.—Samples of normal brain and of slices, after various periods of incubation, were embedded in paraffin and stained with hematoxylin and eosin. In order to detect the histological localization of ferrocyanide in incubated slices a staining technique was adopted, with use of the Prussian blue reaction. Slices were removed from the incubating chamber, washed in Ringer solution, and cut crosswise so as to expose a fresh surface. The segments were then placed in a solution of the following composition:

Formalin	10%
Ferric ammonium sulfate	1%
Hydrochloric acid	1%

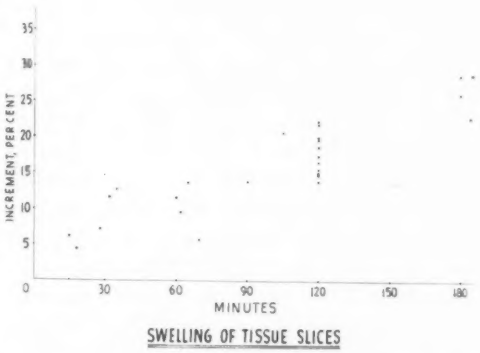
Formation of the colloidal Prussian blue occurred simultaneously with fixation, thereby preventing ferrocyanide from diffusing out. Segments were embedded and sections made off the fresh-cut surface. These were mounted and counterstained with paracarmine.

Tissue Respiration.—Oxygen uptakes of rat brain in a medium of phospate Ringer solution, sodium ferrocyanide, dextrose, and glutamate were determined by the standard techniques with use of a Warburg apparatus.‡ Tissue in this case, however, was in the form of brain brei instead of slices.

RESULTS AND COMMENT

Tissue Swelling.—At best, any technique of incubating tissue slices in vitro introduces a number of abnormal conditions, including such factors as effects of decapitation, trauma of making brain slices, the inevitable sectioning of a great number of axons, and the relatively inefficient penetration of oxygen and nutrient into the specimen. One manifestation of these conditions is the tissue swelling which invariably occurs, and which has been previously commented upon by Stern and co-workers [16] and Elliott.[17] If the degree of swelling be plotted against time of incubation, it will be found that there is an initial rapid gain in weight of the order of 10%, which reaches a plateau within 30 minutes but is succeeded by a steady progressive increase reaching 25% to 30% at 3 hours and in direct proportion to time (Graph 1). If water content in excess of normal be plotted against time, the curve proves to be identical with that of the degree of swelling.

In any experiment concerned with fluid partitions of in vitro tissue slices, it is necessary to define and properly allow for this phenomenon. Since the incubating medium is presumably in direct communication and ultimately in equilibration with the interstitial fluid, then it would follow that the only osmotic differential would be between intracellular fluid and incubating medium; hence, any swelling encountered would have to be predominantly, if not exclusively, on the basis of cellular expansion. When histological preparations of these tissue slices were examined, this was indeed found to be the case. Cytoplasmic swelling of both neurons and glia appeared, minimal at first but becoming increasingly prominent with time of incubation. In some large neurons of cortex and hippocampal formation there was a striking degree of ballooning of nuclei at the expense of cytoplasm. Occasionally, in some of the three-hour specimens it was possible to observe cytoplasmic swelling of perifascicular oligodendroglia and vacuolation in some nerve fibers. In no case was there any enlargement of perivascular spaces or perineuronal spaces or any extracellular vacuole formation.



Graph 1.—Relationship of tissue swelling to time of incubation is plotted, with percentage increase in weight represented on the ordinate. After an initial rapid rise in the first 30 minutes, swelling is seen to proceed in linear relation to time over a 3-hour period.

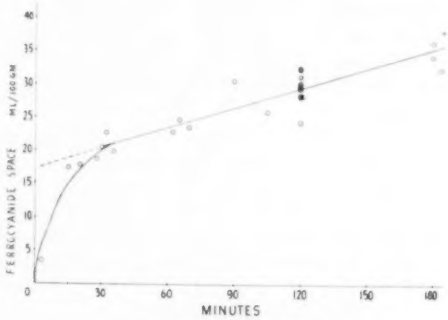
‡ Merck & Company, Rahway, N. J., loaned a Warburg apparatus for this purpose.

Since swelling is found to be in the intracellular compartment, it may be assumed that the extracellular phase remains relatively constant. Consequently, in any quantitation of a substance dissolved in the extracellular space and expressed in terms of milligrams per gram of tissue, it is justifiable to use the original weight of tissue for purposes of calculations rather than the final weight with its intracellular increment. If this be done and the space occupied by a diffusible substance be calculated on the basis of original tissue weight and plotted against time, it would be expected that the "space" should rise to a plateau, there to remain constant. If any further rise should occur, this would have to indicate intracellular leakage of the test substance.

Ferrocyanide Space.—Preliminary experiments were performed to detect the effect of sodium ferrocyanide upon respiration of rat brain, as an indication of any gross toxic effect upon cellular metabolism. Samples of brain brei were incubated in the Warburg apparatus, with control media composed of phosphate Ringer solution plus dextrose and phosphate Ringer solution plus dextrose plus saline. Oxygen uptakes were compared with similar samples incubated in a mixture of Ringer solution plus dextrose plus ferrocyanide. Mean uptake for four controls was 1.18μl per milligram of wet weight per 30 minutes. Mean value for two samples incubated in ferrocyanide was 0.923μl per milligram per 30 minutes. Respiration in vitro, therefore, is not severely inhibited by ferrocyanide but is slightly reduced to about 78% of the control value. This effect was not considered to be toxic to a degree significant to interfere with the type of experiment being undertaken.

Ferrocyanide space was determined in 27 experiments in which time of incubation ranged from five minutes to three hours. The values obtained are shown in Graph 2, with ferrocyanide space on the ordinate and time on the abscissa. It will be seen that there are two distinct components to the curve, that is, a rapid rise in the first 30 minutes followed by a slower rise appearing in simple linear relationship with time. It would be expected that the initial rapid phase represents a diffusion into the readily accessible interstitial space. A slow sustained rise would have to be due to either an expansion of the extracellular compartment or a penetration into cells. On the basis of evidence already cited, there is reason to believe that the latter is the correct hypothesis.

This conclusion was checked by studying histological sections stained for ferrocyanide. It was immediately evident that penetration of ferrocyanide into the deepest zone of the tissue slice did not take place under 30 minutes, but that uniform penetration was attained between 30 and 60 minutes. Sections



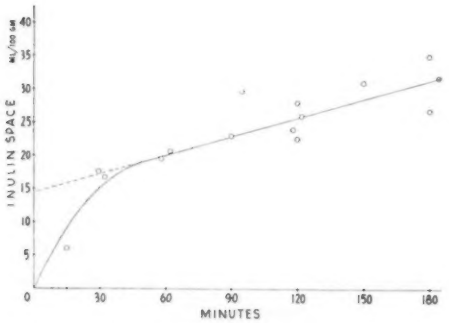
FERROCYANIDE SPACE

Graph 2.—Ferrocyanide space of tissue slices, in milliliters per 100 gm. of tissue, is represented in relation to the time allowed for incubation. There is an abrupt rise within the initial 30 mnutes, followed by a more gradual rise on a simple linear basis. The dotted line is an extrapolation to zero of the straight portion of the curve, with an intersection of the ordinate at 17 ml. per 100 gm.

prepared from slices incubated for this length of time showed a striking distribution of the Prussian blue in blood vessels, in perivascular adventitial spaces, and diffusely throughout the interstitium. Cells were free of the stain, both neurons and glia of the cortex staining red (paracarmine) and appearing sharply demarcated from the pale blue background which penetrated everywhere into the intercellular matrix. In the white matter, myelinated and unmyelinated nerve fibers were likewise unstained by the Prussian blue, but were delicately outlined by the barely visible layers of blue which separated

one fiber from another. In both gray and white matter blood vessels were very prominent, showing the blue stain in adventitia of arteries and veins and as a thin cuff surrounding the finest capillaries. In larger vessels the dye appeared between smooth muscle cells of the media but never penetrated the cell walls.

The appearance, as described, was consistent for all specimens examined. In slices which had been incubated for longer periods, however, another change was seen. Some of the large neurons of cortex and hippocampal formation which showed marked nuclear swelling also showed staining of their cytoplasm by the Prussian blue. This was exceedingly rare at 30 minutes, was less rare



INULIN SPACE

Graph 3.—Relationship of inulin space to incubation time is similar to that of ferrocyanide space in Graph 2, except that the initial rise, representing diffusion into tissue, is slower. An extrapolation to zero minutes intersects the ordinate at 14.5 ml. per 100 gm.

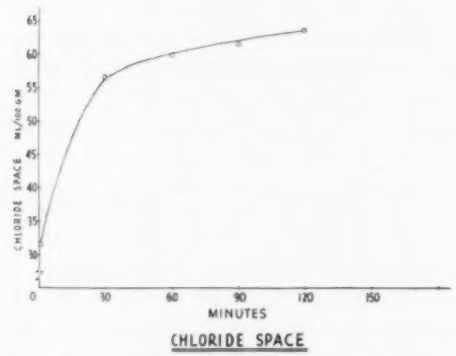
at 2 hours, and fairly frequent by 3 hours. Another type of cellular penetration was seen at the edge of the slice; axones began taking up the ferrocyanide at their cut ends and by three hours showed a gradual penetration in a proximal direction. The conclusions from microscopic examinations, therefore, were that the primary distribution of ferrocyanide is limited to the extracellular phase of brain but that as incubation progresses the compound penetrates into some of the less intact neurons and nerve fibers.

There is, consequently, considerable justification for the assumption that the slow linear phase of Graph 2 does indeed represent an intracellular penetration. This being the case, extrapolation of this linear curve to the ordinate will indicate the volume designated as ferrocyanide space as of zero incubation time, hence in the theoretically normal state. The value obtained is 17 ml. per 100 gm.

Inulin Space.—It was considered desirable to perform comparable experiments using inulin, since this compound has no known toxic effects and since its high molecular weight should make it less likely to penetrate cell membranes. Inulin spaces were determined in 16 experiments at time intervals ranging from 15 minutes to 3 hours. The results are plotted on Graph 3. It will be seen that the general configuration of the curve is similar to that for ferrocyanide but that the initial component representing extracellular penetration is somewhat slower, probably owing to the lower diffusion coefficient of inulin as compared with that of ferrocyanide. The second phase shows a slightly long slope than that for ferrocyanide and this is taken to mean that penetration of inulin into cells is slower. Extrapolation of this linear portion of the curve to the ordinate gives a figure of 14.5 ml. per 100 gm. for inulin space at time zero, a value in good agreement with that obtained by using ferrocyanide.

Chloride Space.—For purposes of comparison, five determinations of chloride spaces were made with groups of tissue slices incubated at intervals from 0 to 120 minutes in a medium composed of phosphate Ringer solution with added dextrose and glutamate. The concentration of chloride in the final medium was 116 mEq. per liter. Results are shown on Graph 4. There is a marked contrast to the curves for ferrocyanide and inulin. The chloride "space," starting at an initial level of 31.5 ml. per 100 gm., rises abruptly by 30 minutes to 56.5 ml. per 100 gm., then continues a slow, steady rise thereafter, reaching a volume of 63 ml. per 100 gm. by 2 hours. Such values are all out of proportion to any possible figure for

brain extracellular volume and indicate that in these conditions of incubation chloride rapidly penetrates into intracellular compartments. This mechanism has not been studied in this series of experiments but on the basis of known data may well be related to derangement of sodium and potassium transport, as well as to changes in other intranuclear and intracytoplasmic components accompanying cell swelling. In any event, chloride space, even when calculated for the normal freshly removed brain and with use of C. S. F. chloride as equilibrated with tissue fluid chloride, proves to be much higher, 31 ml. per 100 gm., than the values obtained for extracellular space by the diffusion method used here.



Graph 4.—Chloride "spaces" of tissue slices incubated in Ringer solution are plotted against time. Distribution "space" of chloride shows a marked rise, approaching 65 ml. per 100 gm.

Fluid Partitions in Rat Brain.—Values derived for the principal fluid compartments of cerebral hemisphere of the rat may be summarized as follows:

Total water	78 ml. per 100 gm.
Extracellular fluid	16 ml. per 100 gm.
Intracellular fluid	62 ml. per 100 gm.

If tissue fluid of rat brain is assumed to be identical with C. S. F. insofar as electrolyte composition is concerned, then it is possible to estimate the approximate composition of fluid compartments in terms of chloride, sodium, and potassium. These values are shown in the accompanying Table and have been derived from figures for electrolyte composition of rat brain as given by various investigators § and by using our own figure for extracellular space.

Summary of Composition of Fluid Compartments

	Concentrations in Extracellular Space mEq./Liter	Concentrations in Intracellular Space mEq./Liter Cell Water
Chloride	120	22.3
Sodium	140	64
Potassium	3.5	162

It is, therefore, contended that a considerable fraction of sodium and chloride exists as intracellular ions in the brain and that the ratio of intracellular concentrations to extracellular concentrations is for chloride 1:5.4, and for potassium 46:1. Theoretically, these two ratios should approach each other as reciprocals in excitable tissues [20]; however, the discrepancy here may well be due to an accumulation of chloride in special phases, such as myelin.

Any expression of intracellular composition for cerebral hemisphere must necessarily be a gross one, including within it not only neurons but glial cells, myelin sheaths, and cells of blood vessel walls. At present, there is no means of differentiating these.

With the material used in these experiments it has not been possible to derive values for extracellular spaces of cortex or white matter separately. In studying slices stained with Prusssian blue, however, it was evident that ferrocyanide was present to a greater degree in cerebral cortex and basal ganglia than in the white matter of corpus callosum or internal capsule. This was particularly notable under a dissecting microscope. Furthermore, in white matter most of the dye was distributed along vascular channels. This sort of evidence, then, suggests that gray matter has a larger extracellular space than does white matter, even as its total water content is higher.

The only estimates of brain extracellular space available for comparison with our own are those obtained by the chloride and sodium methods, which are at least twice as

§ References 1, 18, and 19.

high as our figure. This is not surprising, however, since abundant evidence has now accumulated to show that both electrolytes are in part intracellular. Manery and co-authors || suspected this possibility in their extensive studies upon equilibrations of radioactive chloride and sodium in various tissues. Amberson and co-workers [21] produced evidence that a large fraction of brain chloride did not vary proportionately to serum chloride; hence, it was to be considered nondiffusible. Furthermore, the direct analysis of axoplasm from giant axon of squid by Hodgkin [6] has clearly revealed that sodium and chloride exist intracellularly and in concentration ratios to outside medium of 1:9 to 1:14 respectively.

In respect to extracellular space in other tissues, considerable data have been reported. Thus, for human biopsy muscle Mokotoff and co-workers [5] find an inulin space of 9.8%. Boyle and co-workers,[11] using a diffusion method, report an inulin space for frog sartorius of 9.4%. Creese and Hashish,[22] also using an in vitro inulin diffusion, obtain a value of 26.4% for rat diaphragm. This value compared favorably with a figure of 24%, found by using intravenous inulin injection. For rat gastrocnemius the same authors report an inulin space of 9.6%. With the exception of rat diaphragm, therefore, our value of about 16% for brain is well above the values obtained for skeletal muscle. This is probably related to the fact that total water is greater in cerebral tissue than in muscle.

SUMMARY

The extracellular space of rat cerebrum has been estimated by means of an in vitro diffusion technique with use of ferrocyanide and inulin. The values obtained are 17 and 14.5 ml. per 100 gm., respectively. Histological preparations stained for ferrocyanide have revealed the substance to be uniformly distributed throughout interstitial and perivascular areas of the brain specimens, penetrating cells to only a small degree after prolonged incubation. The values found by this technique are much smaller than those derived from chloride and sodium spaces. It is believed that both sodium and chloride exist as intracellular ions in mammalian brain, and estimations are given for their relative distributions.

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Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

AUTONOMIC HYPOTHALAMIC OUTBURSTS ELICITED BY CEREBELLAR STIMULATION. A. ZANCHETTI and A. ZOCCOLINI, J. Neurophysiol. **17**:475 (Sept.) 1954.

A systematic stimulation of the midline structures of the cerebellum was performed in thalamic cats, and two different patterns of effects were observed. In most animals, when the stimulation was timed to occur during an interval of quiescence of the diencephalic activity, a sudden outburst of sham rage was evoked, including struggling movements, protrusion of the claws, arching of the back, great increase in arterial pressure, hyperpnea, mydriasis, and retraction of the nictitating membrane. At the end of the stimulation the struggling movements were replaced by the known cerebellar postural rebound, and the autonomic manifestations subsided. This response was obtained by stimulation in the rostral and central part of the fastigial nuclei and in the surrounding fibers and folia. The second type of autonomic response was also elicited during the interval of placidity. This consisted in a significant decrease of the arterial blood pressure associated with the classic postural reactions of the limbs and a slight mydriasis. Both hypertension and mydriasis were short-lasting phenomena, generally subsiding before the cessation of the stimulation. A rebound effect with increase in blood pressure, and often a complete outburst of sham rage, were then observed (rebound sham rage). The effective points of stimulation were grouped in the midline fibers between the posterior ends of the roof nuclei and in the buried folia of tuber, pyramis, and uvula.

Both patterns of effects were abolished after destruction of the stimulated regions, leaving unaffected the diencephalic excitability of the animals; since the effects have a low threshold (approximately the same as, or only a little stronger than, that for postural reactions), the authors believe that spread of current is not responsible for the observed effects.

A precollicular decerebration also abolishes both types of autonomic response from cerebellar stimulation. It is suggested that this cerebellar influence on diencephalic structures might be mediated over the ascending reticular formation.

SIEKERT, Rochester, Minn.

CEREBELLAR PROJECTION OF PARAMEDIAN RETICULAR NUCLEUS OF MEDULLA OBLONGATA IN CAT. A. BRODAL and A. TORVIK, J. Neurophysiol. **17**:484 (Sept.) 1954.

A portion of the median reticular formation of the medulla was previously outlined as a particular nucleus, called the paramedian reticular nucleus. It consists of three small cell groups and is found in the space between the hypoglossal root fibers, the raphe, and the inferior olivary nucleus at the level of the middle third of the olivary nucleus. After decerebellations practically all cells of this nucleus disappeared. Retrograde cellular changes in this nucleus were studied after lesions of restricted parts of the cerebellum. All three groups of the paramedian reticular nucleus were found to send fibers to the anterior lobe, the pyramis, and the uvula. No evidence was found of connections with the cortex of the ansoparamedian lobule, the flocculus and paraflocculus, or the dentate nucleus. There appeared to be no topographical correlation between the different groups of the nucleus and the particular portions of the cerebellum.

Apart from this paramedian reticular nucleus, there are only two other cell groups of the reticular formation of the medulla and pons which project onto the cerebellum, namely, the nucleus reticularis lateralis and the nucleus reticularis tegmenti pontis of Bechterew.

Since the inhibition of cortically induced and reflex movements obtainable from the anterior lobe appears to be mediated via the medial reticular formation of the medulla, it is suggested that the cerebellar projection determined in the present study, although not part of this inhibitory center, is functionally closely related to it.

SIEKERT, Rochester, Minn.

DEPOSITS OF FLUORESCENT ACID-FAST PRODUCTS IN THE NERVOUS SYSTEM AND SKELETAL MUSCLES OF ADULT RATS WITH CHRONIC VITAMIN-E DEFICIENCY. L. EINARSON, J. Neurol., Neurosurg. & Psychiat. **16**:98 (May) 1953.

Einarson describes the neuromuscular lesions, in particular, the regular occurrence of deposits of fluorescent, acid-fast products in the nervous system and skeletal muscles of adult rats that have long been kept on a vitamin E-deficient diet. The findings generally confirm the earlier observation and description by Einarson and Riogsted (1938) of these neuromuscular lesions, in particular, of lipid products in the nervous system of adult rats in chronic vitamin E deficiency. The nerve cell changes and the acid-fast deposits are far more widely distributed in the nervous system than was previously realized.

The clinical picture of these animals bears the unmistakable stamp of a neuropathic syndrome, including hyperkinesia, tremors, transient muscular rigidity, increasing hypesthesia and hypalgesia, prominent ataxia and dysmetria, progressive paralyses, and muscular atrophies, which, in the final stage, show a marked symmetrical distribution. Finally, the animals become exhausted and mentally very slow or sluggish. There also occurs a symmetrical loss of hair and other trophic disturbances in the skin (atrophy and ulcerations) and a lowered circulation in the front and hind paws, the skin becoming cooler than usual and cyanotic. Incontinence of the bladder develops in most animals. The whole syndrome is an extremely chronic one. Its onset is insidious after many months on the experimental diet, and it proceeds very slowly; it takes 6 to 15 months from its first appearance to develop completely.

The histological examination shows the disease is due to a combination of neurogenic and myogenic lesions. The lesions consist of degeneration of the dorsal roots and posterior fasciculi of the spinal cord, and myogenic changes in the skeletal muscles, followed by pronounced changes of the visceral and somatic motor and sensory cells of the spinal cord and brain stem, as well as of the cells of the spinal and cranial ganglia; gradually features of the neurogenic muscular atrophy are superimposed on the earlier myogenic changes.

Everywhere, the changes are highly characteristic of the lipid products. Fluorescent acid-fast products appear as fine rounded granules or coarsely globular particles, sometimes coalescing to compact masses. They lie in the cytoplasm of the nerve cells, in or about glial cells and histiocytes, and in the walls of the blood vessels, and they occur almost throughout the nervous system. In the muscles they lie both inside and outside the muscle fibers. They are regularly absent in controls receiving protective doses of vitamin E.

Fluorescent, acid-fast products, comparable to those described in rats, may be observed in human necropsy material, more or less mixed with the commonly occurring lipochrome.

ALPERS, Philadelphia.

Meninges and Blood Vessels

POLYCYSTIC KIDNEY DISEASE AND INTRACRANIAL ANEURYSM. E. F. POUTASSE, J. GARDNER, and L. J. MCCORMACK, J. A. M. A. **154**:741 (Feb. 27) 1954.

The histories of three patients with the combination of congenital intracranial aneurysm and polycystic kidneys are described. The association of these two congenital anomalies appears to be commoner than is generally realized.

All three of these patients were relatively young and entered the hospital because of symptoms of subarachnoid hemorrhage. The first patient, a 29-year-old man, died shortly after admission to the hospital, of a massive intracerebral hemorrhage. At necropsy polycystic kidneys were found. Examination of the circle of Willis showed a small "berry" aneurysm arising from the junction of the anterior communicating and the left anterior cerebral artery.

The second patient, a 27-year-old man, died after an exploratory trephination was performed and a hematoma was evacuated from the right frontal lobe. At necropsy bilateral polycystic kidney was found. A congenital aneurysm of the right middle cerebral artery had ruptured; the resulting hemorrhage had dissected through the cerebral substance into the right lateral ventricle.

The third patient, a 40-year-old woman with the combination of anomalies, in whom the diagnosis of bleeding intracranial aneurysm was established, successfully underwent surgical correction of the aneurysm.

The authors suggest that patients known to have polycystic kidneys who manifest migraine headache or symptoms of cerebrovascular accident should promptly be investigated if intracranial aneurysm is to be discovered in time to offer a chance for survival from hemorrhage. This is especially important in the case of those who have a favorable life expectancy in terms of renal reserve.

ALPERS, Philadelphia.

FAMILIAL INCIDENCE OF CONGENITAL ANEURYSMS OF CEREBRAL ARTERIES. W. R. CHAMBERS, B. F. HARPER JR., and J. R. SIMPSON, J. A. M. A. **155**:358 (May 22) 1954.

It has now been widely accepted that intracranial aneurysms are of a congenital nature. The possibility that there may be a familial factor involved is suggested by this presentation of proved aneurysms in a father and son.

The father, a man of 52, suddenly became unresponsive, thick in speech, and drowsy and complained of a severe headache. Symptoms became progressively worse, and an angiogram revealed an aneurysm in the course of the left middle cerebral artery. At operation a large blood clot was evacuated from the temporal lobe; the aneurysm was found to have a wide, sessile base. Four months after operation the patient was almost ready to return to work. He was attending a speech therapy school in order to overcome a tendency to paraphasia.

Almost exactly two months after the onset of the father's attack, the 21-year-old son had a classic subarachnoid hemorrhage. Carotid angiography was done bilaterally, but no aneurysm could be demonstrated. His condition improved, and he was sent home. A second attack occurred about one month later. At this time his condition was so poor that further angiography was impossible. He died 24 hours after admission. Autopsy revealed an aneurysm of the anterior communicating artery. A blood clot extended down into the pedicle of the sac and evidently stoppered off the aneurysm in such a manner that the angiogram done on the first admission did not show a defect. A new rupture between this clot and the anterior communicating artery had occurred, and wide subarachnoid hemorrhage was present. The presence of a secondary anomaly, a posterior cerebral vessel arising directly from the internal carotid artery, would tend to support the congenital origin of these aneurysms.

ALPERS, Philadelphia.

Diseases of the Brain

CONVULSIVE SEIZURES IN INFANTS WITH PYRIDOXINE-DEFICIENCY DIET. D. B. COURSIN, J. A. M. A. **154**:406 (Jan. 30) 1954.

Coursin describes a syndrome of hyperirritability and convulsive seizures in young infants. A group of 54 such patients was studied from 1951 to 1953. The evidence seems to prove conclusively that these observations occurred in infants fed a liquid S. M. A. preparation, which consisted principally of defatted cow's milk, vegetable and animal fats, and vitamins, plus iron, and contained insufficient pyridoxine (vitamin B_6).

Those patients who received pyridoxine with observed clinical improvement supplied valuable empirical evidence of their need for the vitamin. One patient who experienced status epilepticus that was clinically and electroencephalographically demonstrable and who improved after intramuscular injection of pyridoxine provided the final link in the chain of evidence supporting the syndrome as being the result of a specific deficiency. This case is described in detail.

The manufacturer has added thermostable pure pyridoxine to the new (June, 1953) liquid S. M. A. in an attempt to solve this problem; so far no cases of the syndrome have been reported in infants fed this formula. Additional work seems indicated in order to provide a specific determination of minimal daily requirements for pyridoxine in infancy.

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ASSOCIATION OF MATERNAL AND FETAL FACTORS WITH THE DEVELOPMENT OF EPILEPSY. A. M. LILIENFELD and B. PASAMANICK, J. A. M. A. **155**:719 (June 19) 1954.

The prenatal and paranatal records of 564 epileptic children born in Baltimore between 1935 and 1952 showed significantly more complications of pregnancy and delivery, prematurity, and abnormal neonatal conditions than a similar number of matched controls. These abnormalities were just as frequent among epileptic children whose parents had epilepsy as among those whose parents did not. These epidemiological findings throw some light on the etiology of epilepsy and raise doubts as to the genetic basis of convulsive disorders.

The pattern of factors, such as complications of pregnancy, prematurity, and neonatal abnormalities, that appear to be associated with epilepsy is similar to that previously found to be associated with cerebral palsy, stillbirths, and neonatal deaths. In a previous paper by Lilienfeld and associates, it was postulated that there exists a continuum of reproduction casualty comprising a lethal component of stillbirths and neonatal deaths, and a sublethal component of cerebral palsy. The results of the present study suggest that this sublethal component should also include epilepsy. This observation, together with the fact that approximately one-third of persons with cerebral palsy have convulsive seizures, suggests that cerebral palsy may be a result of a severer type of brain damage than is epilepsy. The results are sufficiently suggestive to warrant the continuance of similar studies concerning other possible components of this continuum. They also warrant serious consideration to the possibilities of establishing concurrent studies in which a group of infants classified by these maternal and fetal factors could be followed, so that one could actually measure the attendant risks of various neurological conditions associated with these maternal and fetal factors.

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CEREBRAL LIPIODAL GRANULOMA. A. MORELLO and I. S. COOPER, Neurology **3**:886 (Dec.) 1953.

The authors point out certain drawbacks which are encountered in the use of intracerebral injection of radiopaque dye to the cutting plane of a prefrontal lobotomy. Such a visualization is not always accurate or adequate. In a series of 100 cases recently reviewed, demonstration of the cutting plane with iodized oil U. S. P. (Lipiodol) was good in 10%, satisfactory in 45%, and unsatisfactory in 45%. Furthermore, the dye is still present months after the injection and tends to diffuse throughout the intracranial cavity.

The case here reported, one of iodized oil granuloma in the frontal lobe, illustrates the fact that the dye may be responsible for serious reactive lesions. The authors describe a technique for roentgenologic visualization of the plane of lobotomy which does not depend upon the use of a contrast medium.

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ACQUIRED EPILEPSY—A STUDY OF 535 CASES. B. SMITH, G. C. ROBINSON, and W. G. LENNOX, Neurology **4**:19 (Jan.) 1954.

This study of 535 noninstitutionalized persons of various ages and economic status emphasizes the wide diversity of conditions, both genetic and acquired, which either alone or in combination may result in some of the various manifestations of epilepsy.

The authors reviewed the records of 1648 patients with a diagnosis of epilepsy. Of these, 535, or 32.4%, gave evidence of organic lesion of the brain acquired prior to the person's first seizure. In 52% the evidence for the pathologic change was believed conclusive; in 48%, only probable. Of the 535 patients, 69% were private, and 31% clinic, patients, the latter being adolescent or younger.

Ninety per cent of patients had the first seizure before the age of 20; 24% had a positive family history of epilepsy. Evidence for a cerebral lesion was furnished in largest proportion, 88%, by the patient's past history, with the electroencephalogram, description of seizures, neurologic examination, and pneumoencephalogram following in order of importance.

The causes of pathologic change were as follows: prenatal, 13.3%; natal conditions, 30.1%; postnatal trauma, 20.7%; injections, 17.2%; other conditions, 6.4%; unassigned, 12.3%.

Data studied with respect to the patient's age at the first seizure showed a progressive decline of paranatal mishaps and progressive increase of postnatal traumatic conditions with increasing age. Nearly one-half of the patients, 46%, had the initial seizure within 12 months after the first etiologic event. In 12% epilepsy did not arise until 10 years or more later. The time interval separating etiology and epilepsy was shorter for postnatal trauma and infections than for paranatal conditions.

The authors point out that the distribution of causes differs radically from a previous series of older patients.

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Diseases of the Spinal Cord

NERVOUS SYSTEM DAMAGE FOLLOWING PARAVERTEBRAL BLOCK WITH EFOCAINE. J. E. BRITTINGHAM, L. N. BERLIN, and H. G. WOLFF, J. A. M. A. **151**:329 (Jan. 23) 1954.

The history of three patients with evidence of spinal cord damage following paravertebral thoracic nerve block with Efocaine (a preparation containing 1% procaine, 0.25% procaine hydro-

chloride, and 5% butyl-*p*-aminobenzoate in a polyethylene-glycol-propylene glycol-water solvent) is reported in this paper. In two of them the "blocks" were accomplished by fully trained anesthesiologists. It seems likely that in each case some Efocaine permeated the subarachnoid space and was there absorbed to produce local myelopathy. In one case, postmortem findings demonstrated extensive damage to the periphery of the cord and dorsal columns.

The authors point out that paravertebral nerve block carries dangers of damage to the nerve tissue that are related to those of spinal anesthesia, but not so great. They conclude that Efocaine is not a safe agent for use in paravertebral nerve blocks.

ALPERS, Philadelphia.

PROTRUDED LUMBAR INTERVERTEBRAL DISKS IN CHILDREN. J. H. WEBB and R. L. KENNEDY, J. A. M. A. **154**:1153 (April 3) 1954.

Of approximately 6500 patients who were operated on for protruded lumbar intervertebral disks at the Mayo Clinic, only 5 (0.077%) were in the period of childhood (less than 16 years of age). The clinical and pathologic features in these five cases do not differ significantly from those in adults who have similar lesions. A history of trauma that could be related to the onset of symptoms was obtained in three of the five cases. As in adults, the physical findings varied from minimal limitation of motion of the back to severe spasm of the erector spinal muscles, changes in reflexes, and neurologic defects.

Multiple protrusions were present in one case, namely, a midline protrusion at the fourth lumbar interspace and a lateral protrusion at the lumbosacral interspace. The protrusions in three of the four remaining cases were at the fourth lumbar interspace. Of these, two were midline in type. In the remaining case, a midline protrusion was present at the lumbosacral interspace. Here, too, these cases parallel the findings in adult patients.

Protruded intervertebral disks are rarely encountered in children, as this study shows. However, the authors point out that the occurrence of low backache and sciatic pain in a child should arouse suspicion of the possible presence of a protruded lumbar intervertebral disk. If other causes of these symptoms can be excluded, myelography and removal of the lesion should be considered, after a thorough trial of conservative therapy has failed to provide relief. All five patients experienced good results from surgical treatment.

ALPERS, Philadelphia.

INTRAUTERINE POLIOMYELITIS INFECTION. M. SCHAEFFER, M. J. FOX, and CHEN P. LI, J. A. M. A. **155**:248 (May 15) 1954.

The authors report a case which demonstrated poliomyelitis virus in both the placenta and the fetus, infected during pregnancy.

The patient, a 24-year-old white woman, was admitted to hospital on the 11th day of illness, 4 days after weakness of her left arm was noted. The examination and laboratory findings are recorded. On the following day a spontaneous abortion occurred, with delivery of a macerated fetus. The mother's postabortive course was uneventful, and she was transferred a week later to another hospital for postpoliomyelitis treatment.

The placenta and fetus were refrigerated and sent for study to the virus laboratory. These studies were done two months later. Preparation from the fetus material was injected into a monkey, and fever developed on the fifth day and paralysis on the seventh. In the monkey receiving placenta material, fever developed on the 10th day and paralysis on the 12th. Both animals showed typical poliomyelitis lesions on postmortem study. The virus isolated from both animals was identified as poliomyelitis virus Type 1.

ALPERS, Philadelphia.

Peripheral and Cranial Nerves

GUILLAIN-BARRÉ SYNDROME OCCURRING DURING CORTISONE THERAPY. H. GRANT and H. N. LEOPOLD, J. A. M. A. **155**:252 (May 15) 1954.

A 33-year-old white woman had been treated with cortisone for severe rheumatoid arthritis for three years and was on the usual maintenance dose of 100 mg. daily. One week before admission to the hospital there developed gastrointestinal symptoms, accompanied by a low-grade fever, and three days later she began having difficulty in walking, generalized weakness, and severe numbness involving both lower extremities and the trunk. On the day of admission both legs were paralyzed, and paralysis of the left facial nerve had developed.

While neurologically the picture suggested hypopotassemia, an electrocardiogram was normal and there was no benefit obtained by giving potassium chloride. Because of the flaccid paralysis with numbness, the preceding gastrointestinal disturbances, the facial paralysis, and the spinal fluid findings, a diagnosis of Guillain-Barré syndrome was made.

During the first week in hospital, the cortisone therapy was stopped, with no apparent benefit and with actual progression of the disease. After the first week, because of increasing arthritic symptoms, cortisone therapy was resumed. After the second week, the patient began to show gradual but sustained improvement. Her deep reflexes returned, and the paralysis in the legs gradually disappeared. The facial paralysis had gone except for slight residual weakness.

The authors suggest that the cortisone had no direct causative bearing on the development of the Guillain-Barré syndrome in this case.

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Treatment, Neurosurgery

CLINICAL EVALUATION OF PRIMIDONE (MYSOLINE), NEW ANTICONVULSANT DRUG. D. SCIARRA, S. CARTER, C. T. VICALE, and H. H. MERRITT, J. A. M. A. **154**:827 (March 6) 1954.

Primidone (Mysoline), 5-phenyl-ethylhexahydro-pyrimidine-4,6 dione, is a new synthetic compound closely related to phenobarbital. Results of its use have been reported previously by four separate groups of clinical investigators. This report describes the use of primidone in 121 patients with one or more types of convulsive seizures. The anticonvulsant effect of the drug could be evaluated in 72 patients, who were observed for periods ranging from 1 to 18 months. In all but seven cases primidone was given in conjunction with one or more of the standard anticonvulsant drugs.

These investigators found that seizures were completely controlled in 10%, reduced in frequency in 43%, and unchanged in 47% of the cases. The greatest benefit occurred when the seizures were of the grand mal, psychomotor, minor, or focal type. No improvement was noted in any of the patients with petit mal. Side-effects occurred in 65 patients, but none were serious. Drowsiness and ataxia were the two most frequent symptoms and made it necessary to discontinue the administration of primidone in 25 patients.

ALPERS, Philadelphia.

VERTEBRAL FRACTURES AS A COMPLICATION OF ELECTROCONVULSIVE THERAPY. P. A. DEWALD, N. M. MARGOLIS, and H. WEINER, J. A. M. A. **154**:981 (March 20) 1954.

The objective of this study was to provide data regarding the following questions: (1) the incidence of fracture of the spine with and without muscle relaxants; (2) the effects of age, sex, bony structure of the spine, and glissando and direct methods of treatment on the fracture incidence; (3) location and severity of fractures, and (4) the incidence of asymptomatic fractures and fractures with minimal transient symptoms. The case material for this study was selected from 1180 men and women admitted to the psychiatric wards of a general hospital. Of these, 263 patients received electroconvulsive therapy.

A total of 285 consecutive courses of electroconvulsive therapy given these patients were studied by means of preshock and postshock roentgenograms to discover the incidence of vertebral fracture. Of 72 courses of E. C. T. given to men and 213 courses given to women, the over-all fracture incidence was 20.8%. The rate for men was 42.9%; for women, 13.7%. Fifty-four patients began E. C. T. with decamethonium bromide (Syncurine), with a resultant fracture incidence of 1.9%. Osteoporosis and the sex of the patient were significant in the incidence of fractures. Age, position of patient, restraint, and method of initiating the current did not influence the fracture incidence.

From these results it would appear that the only variation in technique that affects the incidence of fractures is the use of a muscle relaxant. These data also suggest that muscle relaxants are more effective in prevention of an initial fracture than in arresting the progression of such fracture or in preventing the appearance of a new fracture.

The authors agree with previous studies that have indicated that the presence of these fractures is of little clinical significance in the vast majority of cases. However, it is their practice to use a muscle relaxant prophylactically in those patients whose preshock examination gives findings that would predispose to fracture, such as osteoporosis or large muscle mass.

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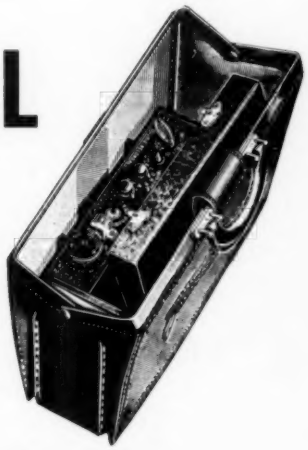

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